STIC Search Report
Biotech-Chem Library

STIC Database Tracking Number: 165678

TO:	From:
Shailendra Kumar Location: 5c03 / 5c18 Wednesday, September 28, 2005 Art Unit: 1621 Phone: 571-272-0640 Serial Number: 10 / 509277	Jan Delaval Location: Biotech-Chem Library Remsen 1a51 Phone: 571-272-2504 jan.delaval@uspto.gov

Search Notes

Access DB# _____

SEARCH REQUEST FORM

16678

Scientific and Technical Information Center

Requester's Full Name: S. Kumar Examiner #: 69594 Date: 9/14/05

Art Unit: 1621 Phone Number 2-0640 Serial Number: 10/509277

Mail Box and Bldg/Room Location: REM 5C03 5C18 Results Format Preferred (circle): PAPER DISK E-MAIL

If more than one search is submitted, please prioritize searches in order of need.

****

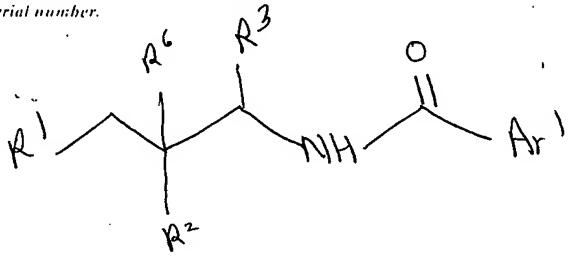
Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of invention: Substituted aryl amides

Inventors (please provide full names): William Hagmann et. al.

Earliest Priority Filing Date: 4/5/2002

**For Sequence Searches Only* Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.*



R1 is alkyl, cycloalkyl, aryl, heteroaryl etc.

R2 is cycloalkyl, aryl, heteroaryl, OR, NRR, CO_2R etc.

R3 is H, alkyl

R6 is H, alkyl, OR, CN, Hal, NRR etc.

Ar1 is aryl, heteroaryl (subst/unsubst.)

Please see claims.

****

STAFF USE ONLY	Type of Search	Vendors and cost where applicable
Searcher:	NA Sequence (#)	STN ✓
Searcher Phone #: 22804	AA Sequence (#)	Dialog
Searcher Location:	Structure (#) ✓	Questel/Orbit
Date Searcher Picked Up: 9/27/05	Bibliographic	Dr.Link
Date Completed: 9/28/05	Litigation	Lexis/Nexis
Searcher Prep & Review Time	Fulltext	Sequence Systems
Clerical Prep Time: 60	Patent Family	WWW/Internet
Online Time: +180	Other	Other (specify)

PTO-1590 (8-01)

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=> fil reg
FILE 'REGISTRY' ENTERED AT 09:02:53 ON 28 SEP 2005
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
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Property values tagged with IC are from the ZIC/VINITI data file
provided by InfoChem.

STRUCTURE FILE UPDATES:   27 SEP 2005  HIGHEST RN 864057-55-6
DICTIONARY FILE UPDATES:  27 SEP 2005  HIGHEST RN 864057-55-6

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH JULY 14, 2005

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

**********************************************************************
*                                                                    *
* The CA roles and document type information have been removed from *
* the IDE default display format and the ED field has been added,    *
* effective March 20, 2005.  A new display format, IDERL, is now     *
* available and contains the CA role and document type information. *
*                                                                    *
**********************************************************************

Structure search iteration limits have been increased.  See HELP SLIMITS
for details.

Experimental and calculated property data are now available. For more
information enter HELP PROP at an arrow prompt in the file or refer
to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html

=> d sta que l80
L71             STR
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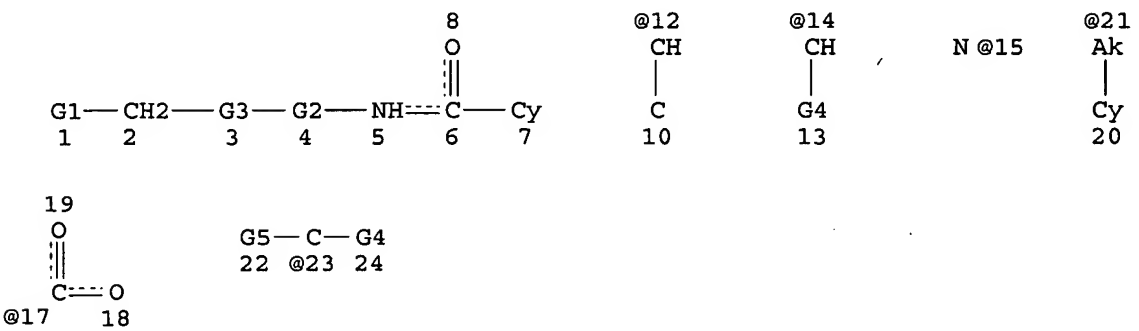


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VAR G1=C/CY
VAR G2=CH2/12
VAR G3=14/23
VAR G4=CY/21/O/15/17
VAR G5=C/O/X/CN/15
NODE ATTRIBUTES:
NSPEC   IS RC     AT  15
DEFAULT MLEVEL IS ATOM
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```
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS  21

STEREO ATTRIBUTES: NONE
L73             SCR 1126 OR 1235
L75             SCR 2039 OR 2041 OR 2127 OR 2050 OR 2049 OR 2048 OR 2053 O
R 2052 OR 2051 OR 2043 OR 2054 OR 1918
L80           1 SEA FILE=REGISTRY SSS SAM L71 AND L73 NOT L75

  1.4% PROCESSED    2000 ITERATIONS                              1 ANSWERS
INCOMPLETE SEARCH (SYSTEM LIMIT EXCEEDED)
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE  **INCOMPLETE**
                        BATCH   **INCOMPLETE**
PROJECTED ITERATIONS:      2881436 TO  2926364
PROJECTED ANSWERS:             940 TO     1962



=> d sta que l81
L71             STR
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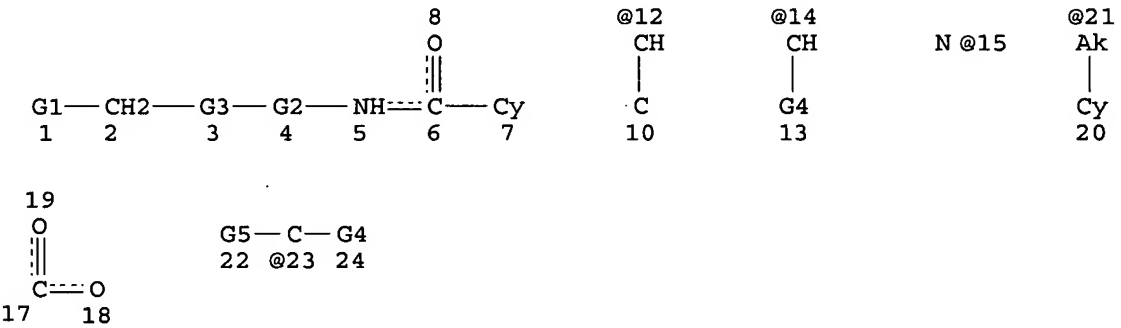


```
VAR G1=C/CY
VAR G2=CH2/12
VAR G3=14/23
VAR G4=CY/21/O/15/17
VAR G5=C/O/X/CN/15
NODE ATTRIBUTES:
NSPEC   IS RC     AT  15
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS  21

STEREO ATTRIBUTES: NONE
L74             SCR 1992 AND 2004 AND 1838 AND 95 AND 164
L75             SCR 2039 OR 2041 OR 2127 OR 2050 OR 2049 OR 2048 OR 2053 O
R 2052 OR 2051 OR 2043 OR 2054 OR 1918
L81           6 SEA FILE=REGISTRY SSS SAM L71 AND L74 NOT L75

  2.1% PROCESSED    2000 ITERATIONS                              6 ANSWERS
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INCOMPLETE SEARCH (SYSTEM LIMIT EXCEEDED)
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE  **INCOMPLETE**
                        BATCH   **INCOMPLETE**
PROJECTED ITERATIONS:      1891412 TO  1928068
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=> d sta que l76
L71             STR
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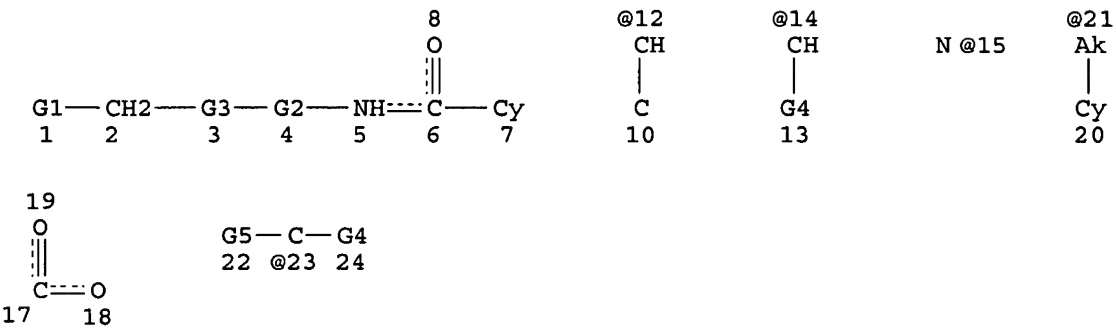


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VAR G1=C/CY
VAR G2=CH2/12
VAR G3=14/23
VAR G4=CY/21/O/15/17
VAR G5=C/O/X/CN/15
NODE ATTRIBUTES:
NSPEC   IS RC     AT  15
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS  21

STEREO ATTRIBUTES: NONE
L73             SCR 1126 OR 1235
L74             SCR 1992 AND 2004 AND 1838 AND 95 AND 164
L75             SCR 2039 OR 2041 OR 2127 OR 2050 OR 2049 OR 2048 OR 2053 O
R 2052 OR 2051 OR 2043 OR 2054 OR 1918
L76           0 SEA FILE=REGISTRY SSS SAM L71 AND L73 AND L74 NOT L75

  2.2% PROCESSED    2000 ITERATIONS                          0 ANSWERS
INCOMPLETE SEARCH (SYSTEM LIMIT EXCEEDED)
SEARCH TIME: 00.00.01

FULL FILE PROJECTIONS:  ONLINE  **INCOMPLETE**
                        BATCH   **INCOMPLETE**
PROJECTED ITERATIONS:      1822121 TO  1858119
PROJECTED ANSWERS:               0 TO        0



=> d his
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               DEL HIS

     FILE 'REGISTRY' ENTERED AT 07:22:04 ON 28 SEP 2005
L1            64 SEA FILE=REGISTRY ABB=ON  PLU=ON  (L*** OR L*** OR L*** OR L*** OR L
L2           285 SEA FILE=REGISTRY ABB=ON  PLU=ON  L*** NOT L***
L3             4 S L2 AND NCNC2/ES
L4             3 S L2 AND NCNC2-C6/ES
L5             2 S L2 AND SC4/ES
L6             2 S L2 AND NCSC2/ES
L7             2 S 616243-33-5 OR 616243-43-7
L8             2 S L2 AND CARBAZOL?
L9             1 S 616243-71-1
L10            1 S L8 AND 1/NC
L11            2 S L2 AND PYRIDO?
L12            4 S L2 AND PYRAZOL? AND PYRIMID?
L13            2 S L12 AND 2/NC
L14            2 S 616243-78-8 OR 616243-76-6
L15            2 S L12 AND 1/NC
L16            2 S L2 AND PYRIDO? AND PYRIMIDIN?
L17            2 S L2 AND IMIDAZO? AND PYRIDIN?
L18            1 S 616243-98-2
L19            1 S L17 AND 1/NC
L20            2 S L2 AND SC4-OC2OC2/ES
L21            6 S L2 AND NAPHTH?
L22            3 S L21 AND 2/NC
L23            3 S 616244-22-5 OR 616243-90-4 OR 616243-29-9
L24            3 S L21 AND 1/NC
L25           52 S L2 AND NC5/ES NOT L3-L24
L26           19 S L25 AND C6/ES AND NR>=3
L27            9 S L26 AND 1/NC
L28           10 S L26 NOT L27
L29            5 S 616243-35-7 OR 616243-53-9 OR 616243-55-1 OR 616243-57-3 OR 6
L30            5 S 616244-02-1 OR 616244-06-5 OR 616244-15-6 OR 616244-20-3 OR 6
L31           32 S L2 AND 46.150.18/RID AND 3/NR NOT L3-L30
L32           23 S L31 AND 1/NC
L33           23 S L32 AND 4 CHLOROPHENYL
L34            8 S L33 AND BIS
L35           15 S L33 NOT L34
L36            9 S L31 NOT L32-L35
L37           32 S L2 AND 46.150.18/RID AND 4/NR NOT L3-L36
L38           14 S L37 AND 1/NC
L39           68 S L3,L4,L7,L9,L10,L14-L16,L18-L20,L23,L24,L27,L
L40           18 S L37 NOT L38,L39
L41            7 S 616244-28-1 OR 616244-32-7 OR 616244-12-3 OR 616244-24-7 OR 6
L42            9 S 616243-37-9 OR 616243-39-1 OR 616243-41-5 OR 616243-48-2 OR 6
L43           84 S L39,L41,L42
L44           63 S L1 AND 1/NC
L45          138 S L43,L44
                 SEL RN
L46           42 S E1-E138/CRN
L47          179 S L45,L46
                 SAV L47 KUMAR509B/A
L48          140 S L2 NOT L1,L3-L47

     FILE 'HCAOLD' ENTERED AT 08:40:41 ON 28 SEP 2005
L49            0 S L47

     FILE 'HCAPLUS' ENTERED AT 08:40:44 ON 28 SEP 2005
L50            1 S L47
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                E HAGMANN/AU
                E HAGMANN 2/AU
                E HAGMANN W/AU
L51         180 S E3-E7
                E LIN L/AU
L52         279 S E3
                E LIN L S/AU
L53          27 S E3
                E LIN LINUS/AU
L54          29 S E3-E5
                E SHAH/AU
L55           1 S E3
                E SHAH S/AU
L56         148 S E3
L57          37 S E25
                E SHAH SHRENIK/AU
L58         101 S E3-E5
                E SHRENIK/AU
L59           1 S E4
                E KANTILAL/AU
L60           1 S L50 AND L51-L59
L61           1 S L50 AND MERCK?/PA,CS
L62           1 S L50,L60,L61

     FILE 'REGISTRY' ENTERED AT 08:43:33 ON 28 SEP 2005
L63           4 S 616243-32-4 OR 616243-93-7 OR 616243-95-9 OR 616244-19-0
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L64         183 S L47,L63
L65           4 S 616244-18-9 OR 616243-94-8 OR 616243-92-6 OR 616243-31-3
L66         187 S L64,L65
                SAV L66 KUMAR509B/A

     FILE 'HCAOLD' ENTERED AT 08:45:28 ON 28 SEP 2005
L67           0 S L66

     FILE 'HCAPLUS' ENTERED AT 08:45:32 ON 28 SEP 2005
L68           1 S L66
L69           1 S L62,L68

     FILE 'USPATFULL' ENTERED AT 08:45:41 ON 28 SEP 2005
L70           1 S L66

     FILE 'HCAPLUS' ENTERED AT 08:46:05 ON 28 SEP 2005

     FILE 'USPATFULL' ENTERED AT 08:46:20 ON 28 SEP 2005

     FILE 'REGISTRY' ENTERED AT 08:46:46 ON 28 SEP 2005
L71             STR
L72           3 S L71
L73             SCR 1126 OR 1235
L74             SCR 1992 AND 2004 AND 1838 AND 95 AND 164
L75             SCR 2039 OR 2041 OR 2127 OR 2050 OR 2049 OR 2048 OR 2053 OR 205
L76           0 S L71 AND L73 AND L74 NOT L75 SAM
L77           2 S L71 AND L73 AND L74 SAM
L78             SCR 1199
L79           5 S L71 AND L73 AND L74 AND L78 SAM
L80           1 S L71 AND L73 NOT L75 SAM
L81           6 S L71 AND L74 NOT L75 SAM

     FILE 'REGISTRY' ENTERED AT 09:02:53 ON 28 SEP 2005
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FILE 'HCAPLUS' ENTERED AT 08:46:05 ON 28 SEP 2005
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FILE COVERS 1907 - 28 Sep 2005  VOL 143 ISS 14
FILE LAST UPDATED: 27 Sep 2005  (20050927/ED)

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 This file contains CAS Registry Numbers for easy and accurate
 substance identification.

=> d 169 bib abs hitrn fhitstr retable

L69  ANSWER 1 OF 1  HCAPLUS  COPYRIGHT 2005 ACS on STN
AN   2003:837028  HCAPLUS
DN   139:337785
TI   Preparation of substituted arylamides as cannabinoid-1 receptor
     antagonists and/or inverse agonists for use as psychotropic drugs
IN   Hagmann, William K.; Lin, Linus S.; Shah, Shrenik
     K.
PA   Merck & Co., Inc., USA
SO   PCT Int. Appl., 191 pp.
     CODEN: PIXXD2
DT   Patent
LA   English
FAN.CNT 1
     PATENT NO.          KIND   DATE        APPLICATION NO.         DATE
     ---------------     ----   --------    --------------------    --------
PI   WO 2003087037        A1     20031023    WO 2003-US9800          20030401
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
             CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
             GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS,
             LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH,
             PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ,
             UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
         RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
             KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES,
             FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR,
             BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
     CA 2480856            AA     20031023    CA 2003-2480856         20030401
     EP 1494997            A1     20050112    EP 2003-746565          20030401
         R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
             IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK
     US 2005154202         A1     20050714    US 2003-509277          20030401
     JP 2005527586         T2     20050915    JP 2003-583993          20030401
PRAI US 2002-370553P       P      20020405
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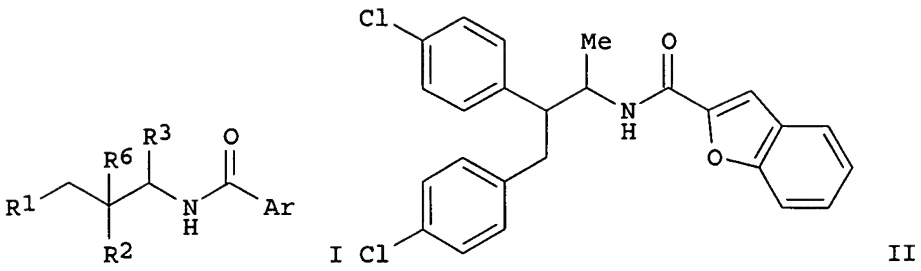
WO 2003-US9800 W 20030401
OS MARPAT 139:337785
GI



AB Title compds. I [wherein R1 = (un)substituted alkyl, (hetero)cycloalkyl, or (hetero)aryl; R2 = (un)substituted (hetero)cycloalkyl, (hetero)aryl, ORd, NRcRd, or CO2Rd; R3 = H or (un)substituted alkyl; R6 = H, halo, CN, NRcRd, or (un)substituted alkyl, alkenyl, or alkynyl; Ar = (un)substituted (hetero)aryl; Rc and Rd = independently H or (un)substituted alkyl, alkenyl, alkynyl, (hetero)cycloalkyl(alkyl), or (hetero)aryl(alkyl); or NRcRd = (un)substituted heterocyclyl; or two ORc groups together with the atoms to which they are attached = (un)substituted heterocyclyl; with provisos; and pharmaceutically acceptable salts thereof] were prepared by conventional and automated synthesis methods as antagonists and/or inverse agonists of the cannabinoid-1 (CB1) receptor (no data). For example, 2,3-bis(4-chlorophenyl)-1-methylpropylamine•HCl was acylated with 2-benzofurancarboxylic acid in the presence of PyBop and TEA in CH2Cl2 to give the desired amide II. I and their pharmaceutical compns. are useful as psychotropic drugs in the treatment of psychosis, memory deficits, cognitive disorders, migraine, neuropathy, neuroinflammatory disorders, including multiple sclerosis and Guillain-Barre syndrome, and the inflammatory sequelae of viral encephalitis, cerebral vascular accidents, and head trauma, anxiety disorders, stress, epilepsy, Parkinson's disease, movement disorders, and schizophrenia (no data). In addition, I and their pharmaceutical compns. are useful for the treatment of substance abuse disorders, the treatment of obesity or eating disorders, as well as the treatment of asthma, constipation, chronic intestinal pseudo-obstruction, and cirrhosis of the liver (no data).

IT **616243-24-4P 616243-25-5P 616243-26-6P**
616243-28-8P 616243-30-2P 616243-32-4P
616243-34-6P 616243-36-8P 616243-38-0P
616243-40-4P 616243-42-6P 616243-44-8P
616243-45-9P 616243-47-1P 616243-49-3P
616243-50-6P 616243-51-7P 616243-52-8P
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616245-06-8P 616245-07-9P 616245-08-0P
616245-09-1P 616245-10-4P 616245-11-5P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(CB1 receptor modulator; preparation of substituted arylamides as CB1 receptor antagonists and/or inverse agonists for use as psychotropic drugs)

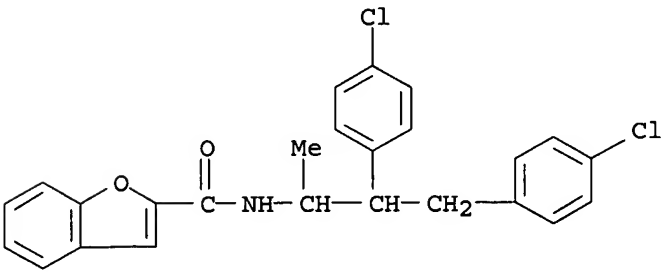
IT **616243-24-4P**

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(CB1 receptor modulator; preparation of substituted arylamides as CB1 receptor antagonists and/or inverse agonists for use as psychotropic drugs)

RN 616243-24-4 HCAPLUS

CN 2-Benzofurancarboxamide, N-[2,3-bis(4-chlorophenyl)-1-methylpropyl]- (9CI) (CA INDEX NAME)



RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Able & Imray	1962			GB 899556 A	HCAPLUS
Haseltine Lake & Co	1969			GB 1172346 A	HCAPLUS
Lack, L	1963	139	248	J Pharm Exp Thera	HCAPLUS

=> fil uspatful
FILE 'USPATFULL' ENTERED AT 08:46:20 ON 28 SEP 2005
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FILE COVERS 1971 TO PATENT PUBLICATION DATE: 27 Sep 2005 (20050927/PD)
FILE LAST UPDATED: 27 Sep 2005 (20050927/ED)
HIGHEST GRANTED PATENT NUMBER: US6951031
HIGHEST APPLICATION PUBLICATION NUMBER: US2005210555
CA INDEXING IS CURRENT THROUGH 27 Sep 2005 (20050927/UPCA)
ISSUE CLASS FIELDS (/INCL) CURRENT THROUGH: 27 Sep 2005 (20050927/PD)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Aug 2005
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Aug 2005

>>> USPAT2 is now available. USPATFULL contains full text of the <<<
>>> original, i.e., the earliest published granted patents or <<<
>>> applications. USPAT2 contains full text of the latest US <<<
>>> publications, starting in 2001, for the inventions covered in <<<
>>> USPATFULL. A USPATFULL record contains not only the original <<<
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>>> are displayed in the PI (Patent Information) field of USPATFULL <<<
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>>> /PK, etc. <<<

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>>> through the new cluster USPATALL. Type FILE USPATALL to <<<
>>> enter this cluster. <<<
>>> <<<
>>> Use USPATALL when searching terms such as patent assignees, <<<
>>> classifications, or claims, that may potentially change from <<<
>>> the earliest to the latest publication. <<<

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substance identification.

=> d l70 bib abs hitrn fhitstr

L70 ANSWER 1 OF 1 USPATFULL on STN
AN 2005:178121 USPATFULL
TI Substituted aryl amides
IN Hagmann, William K., Westfield, NJ, UNITED STATES
Lin, Linus S., Westfield, NJ, UNITED STATES
Shah, Shrenik K., Metuchen, NJ, UNITED STATES
PI US 2005154202 A1 20050714
AI US 2003-509277 A1 20030401 (10)
WO 2003-US9800 20030401
PRAI US 2003-370553P 20020405 (60)
DT Utility
FS APPLICATION
LREP MERCK AND CO., INC, P O BOX 2000, RAHWAY, NJ, 07065-0907, US

CLMN Number of Claims: 25
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 5189
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Novel compounds of structural formula (I) are antagonists and/or inverse agonists of the Cannabinoid-1 (CB1) receptor and are useful in the treatment, prevention and suppression of diseases mediated by the CB1 receptor. The compounds of the present invention are useful as psychotropic drugs in the treatment of psychosis, memory deficits, cognitive disorders, migraine, neuropathy, neuro-inflammatory disorders including multiple sclerosis and Guillain-Barre syndrome and the inflammatory sequelae of viral encephalitis, cerebral vascular accidents, and head trauma, anxiety disorders, stress, epilepsy, Parkinson's disease, movement disorders, and schizophrenia. The compounds are also useful for the treatment of substance abuse disorders, the treatment of obesity or eating disorders, as well as, the treatment of asthma, constipation, chronic intestinal pseudo-obstruction, and cirrhosis of the liver.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.
IT **616243-24-4P 616243-25-5P 616243-26-6P**
616243-28-8P 616243-30-2P 616243-32-4P
616243-34-6P 616243-36-8P 616243-38-0P
616243-40-4P 616243-42-6P 616243-44-8P
616243-45-9P 616243-47-1P 616243-49-3P
616243-50-6P 616243-51-7P 616243-52-8P
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616243-81-3P 616243-83-5P 616243-84-6P
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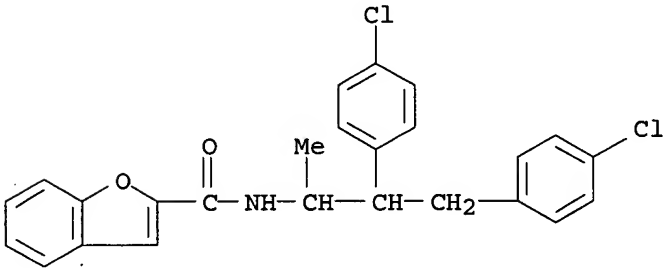
616245-09-1P 616245-10-4P 616245-11-5P
(CB1 receptor modulator; preparation of substituted arylamides as CB1 receptor antagonists and/or inverse agonists for use as psychotropic drugs)

IT **616243-24-4P**
(CB1 receptor modulator; preparation of substituted arylamides as CB1 receptor antagonists and/or inverse agonists for use as psychotropic drugs)

RN 616243-24-4 USPATFULL
CN 2-Benzofurancarboxamide, N-[2,3-bis(4-chlorophenyl)-1-methylpropyl]- (9CI) (CA INDEX NAME)



=> fil reg
FILE 'REGISTRY' ENTERED AT 08:46:46 ON 28 SEP 2005
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PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
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STRUCTURE FILE UPDATES: 27 SEP 2005 HIGHEST RN 864057-55-6
DICTIONARY FILE UPDATES: 27 SEP 2005 HIGHEST RN 864057-55-6

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH JULY 14, 2005

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****
* *
* The CA roles and document type information have been removed from *
* the IDE default display format and the ED field has been added, *
* effective March 20, 2005. A new display format, IDERL, is now *
* available and contains the CA role and document type information. *
* *

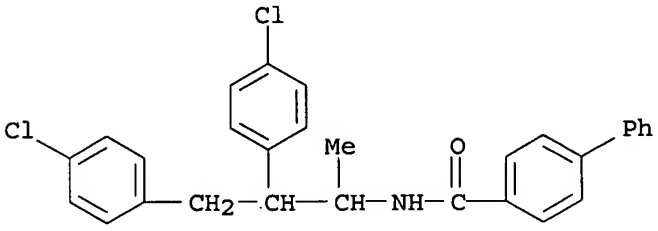
****

Structure search iteration limits have been increased. See HELP SLIMITS for details.

Experimental and calculated property data are now available. For more information enter HELP PROP at an arrow prompt in the file or refer to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html

=> d scan l66

L66 187 ANSWERS REGISTRY COPYRIGHT 2005 ACS on STN
IN [1,1'-Biphenyl]-4-carboxamide, N-[2,3-bis(4-chlorophenyl)-1-methylpropyl]-(9CI)
MF **C29 H25 Cl2 N O**

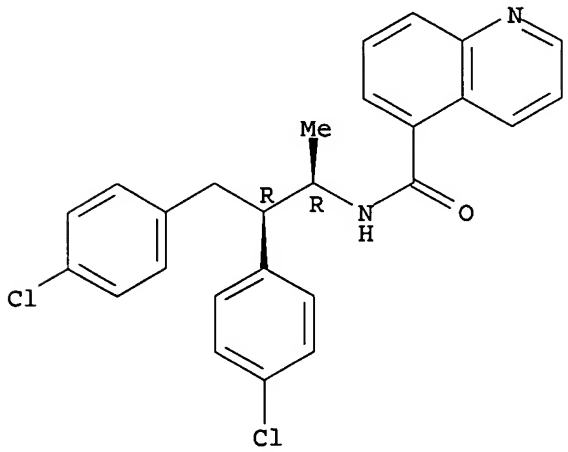


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):25

L66 187 ANSWERS REGISTRY COPYRIGHT 2005 ACS on STN
IN 5-Quinolinecarboxamide, N-[(1R,2R)-2,3-bis(4-chlorophenyl)-1-methylpropyl]-, rel- (9CI)
MF **C26 H22 Cl2 N2 O**
CI COM

Relative stereochemistry.

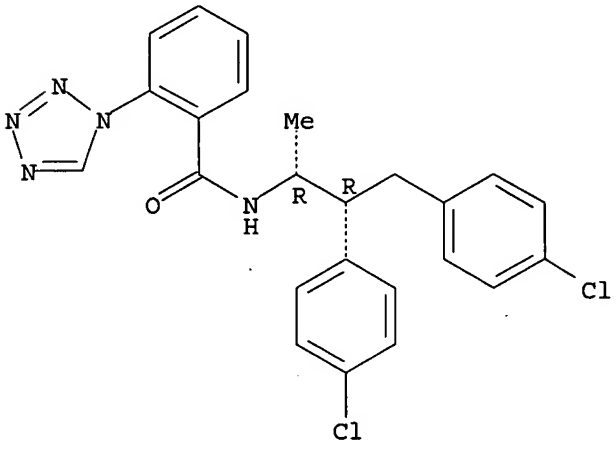


Samples

PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

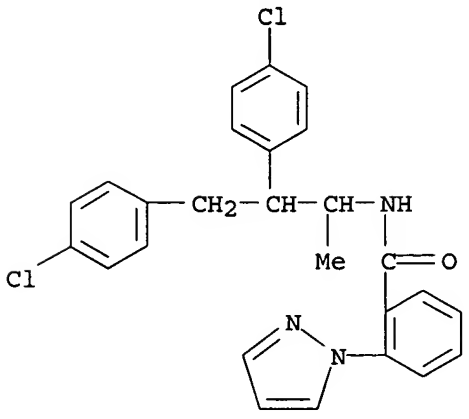
L66 187 ANSWERS REGISTRY COPYRIGHT 2005 ACS on STN
IN Benzamide, N-[(1R,2R)-2,3-bis(4-chlorophenyl)-1-methylpropyl]-2-(1H-tetrazol-1-yl)-, rel- (9CI)
MF C24 H21 Cl2 N5 O
CI COM

Relative stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

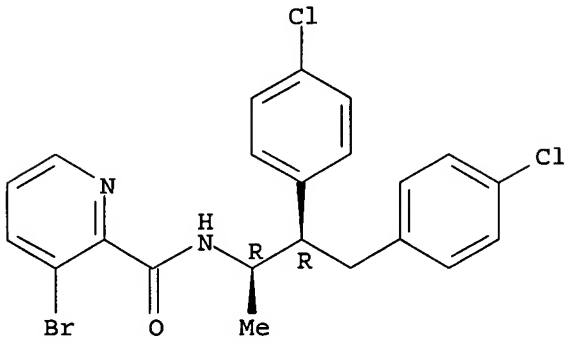
L66 187 ANSWERS REGISTRY COPYRIGHT 2005 ACS on STN
IN **Benzamide, N-[2,3-bis(4-chlorophenyl)-1-methylpropyl]-2-(1H-pyrazol-1-yl)- (9CI)**
MF **C26 H23 Cl2 N3 O**



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L66 187 ANSWERS REGISTRY COPYRIGHT 2005 ACS on STN
IN 2-Pyridinecarboxamide, N-[(1R,2R)-2,3-bis(4-chlorophenyl)-1-methylpropyl]-3-bromo-, rel- (9CI)
MF C22 H19 Br Cl2 N2 O
CI COM

Relative stereochemistry.

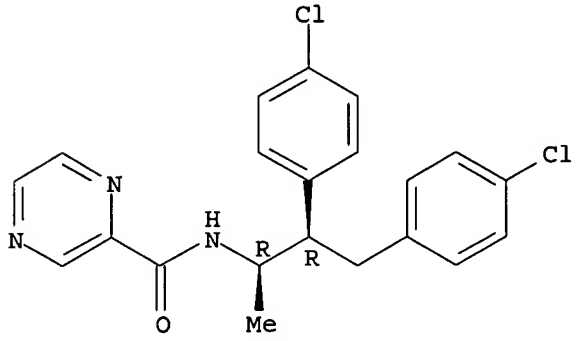


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

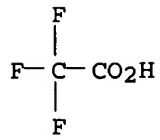
L66 187 ANSWERS REGISTRY COPYRIGHT 2005 ACS on STN
IN Pyrazinecarboxamide, N-[(1R,2R)-2,3-bis(4-chlorophenyl)-1-methylpropyl]-, rel-, trifluoroacetate (9CI)
MF C21 H19 Cl2 N3 O . x C2 H F3 O2

CM 1

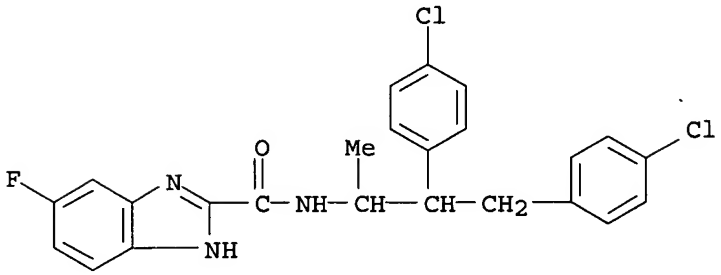
Relative stereochemistry.



CM 2



L66 187 ANSWERS REGISTRY COPYRIGHT 2005 ACS on STN
IN 1H-Benzimidazole-2-carboxamide, N-[2,3-bis(4-chlorophenyl)-1-methylpropyl]-5-fluoro- (9CI)
MF **C24 H20 Cl2 F N3 O**

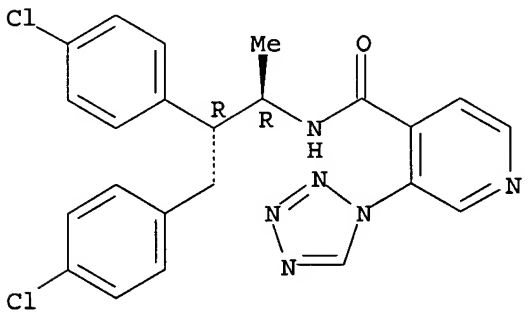


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

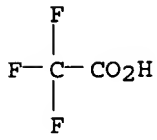
L66 187 ANSWERS REGISTRY COPYRIGHT 2005 ACS on STN
IN 4-Pyridinecarboxamide, N-[(1R,2R)-2,3-bis(4-chlorophenyl)-1-methylpropyl]-3-(1H-tetrazol-1-yl)-, rel-, trifluoroacetate (9CI)
MF C23 H20 Cl2 N6 O . x C2 H F3 O2

CM 1

Relative stereochemistry.



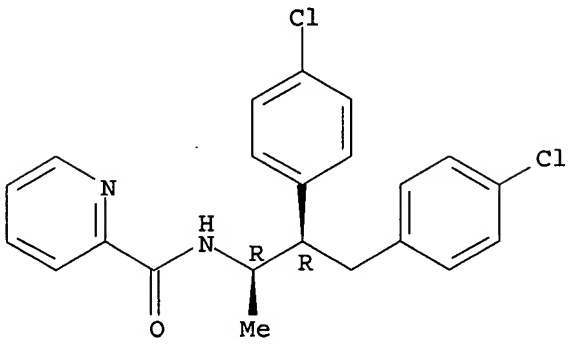
CM 2



L66 187 ANSWERS REGISTRY COPYRIGHT 2005 ACS on STN
IN 2-Pyridinecarboxamide, N-[(1R,2R)-2,3-bis(4-chlorophenyl)-1-methylpropyl]-

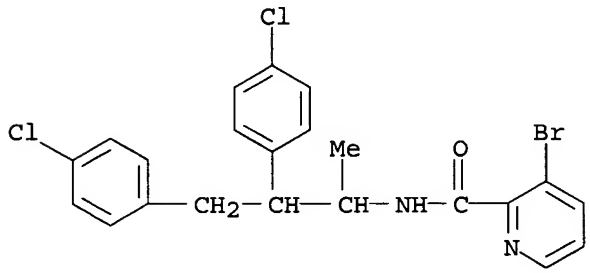
, rel- (9CI)
MF C22 H20 Cl2 N2 O
CI COM

Relative stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L66 187 ANSWERS REGISTRY COPYRIGHT 2005 ACS on STN
IN 2-Pyridinecarboxamide, N-[2,3-bis(4-chlorophenyl)-1-methylpropyl]-3-bromo- (9CI)
MF **C22 H19 Br Cl2 N2 O**

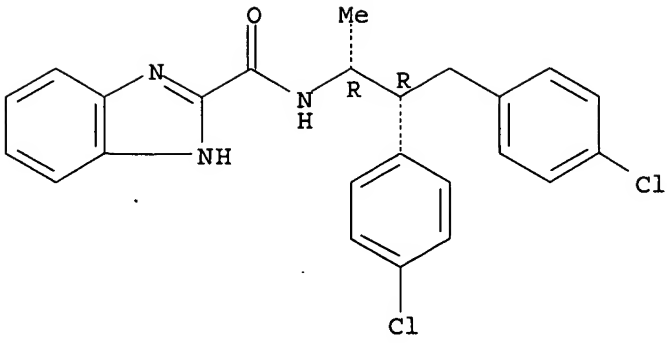


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

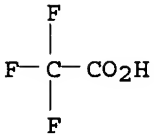
L66 187 ANSWERS REGISTRY COPYRIGHT 2005 ACS on STN
IN 1H-Benzimidazole-2-carboxamide, N-[(1R,2R)-2,3-bis(4-chlorophenyl)-1-methylpropyl]-, rel-, mono(trifluoroacetate) (9CI)
MF C24 H21 Cl2 N3 O . C2 H F3 O2

CM 1

Relative stereochemistry.

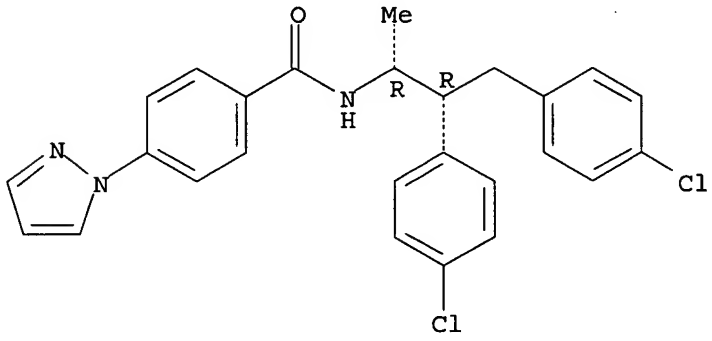


CM 2



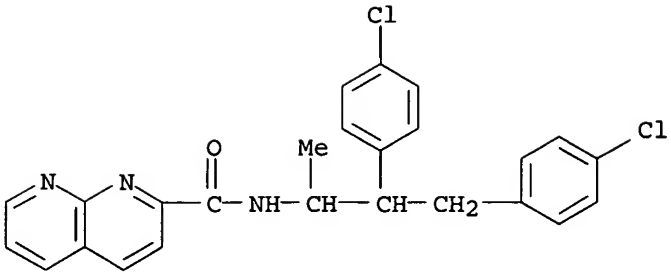
L66 187 ANSWERS REGISTRY COPYRIGHT 2005 ACS on STN
IN Benzamide, N-[(1R,2R)-2,3-bis(4-chlorophenyl)-1-methylpropyl]-4-(1H-pyrazol-1-yl)-, rel- (9CI)
MF C26 H23 Cl2 N3 O
CI COM

Relative stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

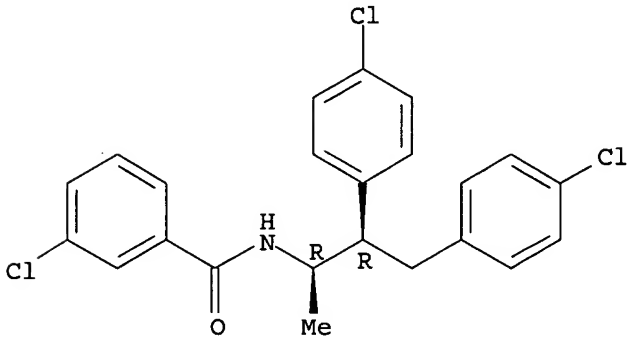
L66 187 ANSWERS REGISTRY COPYRIGHT 2005 ACS on STN
IN **1,8-Naphthyridine-2-carboxamide, N-[2,3-bis(4-chlorophenyl)-1-methylpropyl]- (9CI)**
MF **C25 H21 Cl2 N3 O**



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L66 187 ANSWERS REGISTRY COPYRIGHT 2005 ACS on STN
IN **Benzamide, N-[(1R,2R)-2,3-bis(4-chlorophenyl)-1-methylpropyl]-3-chloro-, rel- (9CI)**
MF **C23 H20 Cl3 N O**

Relative stereochemistry.

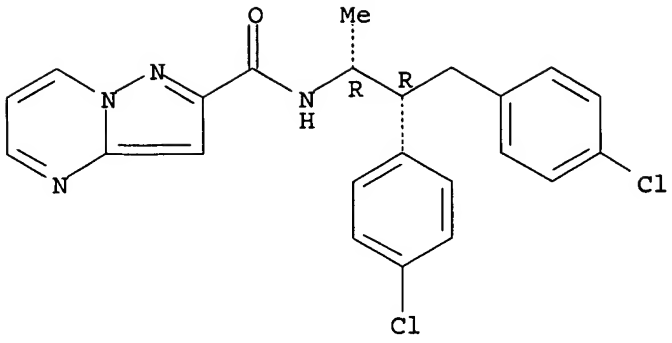


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

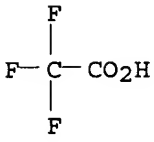
L66 187 ANSWERS REGISTRY COPYRIGHT 2005 ACS on STN
IN Pyrazolo[1,5-a]pyrimidine-2-carboxamide, N-[(1R,2R)-2,3-bis(4-chlorophenyl)-1-methylpropyl]-, rel-, trifluoroacetate (9CI)
MF C23 H20 Cl2 N4 O . x C2 H F3 O2

CM 1

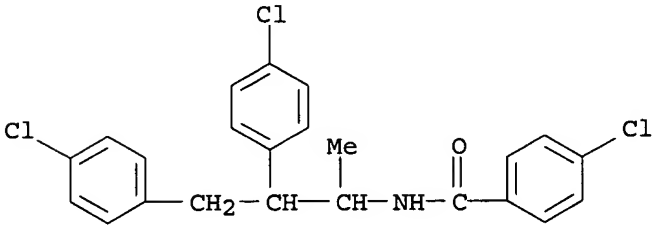
Relative stereochemistry.



CM 2

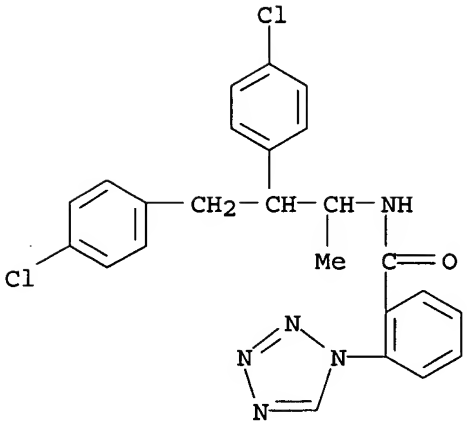


L66 187 ANSWERS REGISTRY COPYRIGHT 2005 ACS on STN
IN **Benzamide, N-[2,3-bis(4-chlorophenyl)-1-methylpropyl]-4-chloro- (9CI)**
MF **C23 H20 Cl3 N O**



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L66 187 ANSWERS REGISTRY COPYRIGHT 2005 ACS on STN
IN **Benzamide, N-[2,3-bis(4-chlorophenyl)-1-methylpropyl]-2-(1H-tetrazol-1-yl)- (9CI)**
MF **C24 H21 Cl2 N5 O**

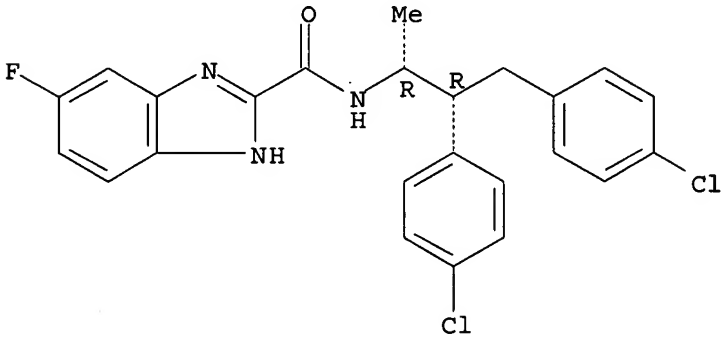


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L66 187 ANSWERS REGISTRY COPYRIGHT 2005 ACS on STN
IN 1H-Benzimidazole-2-carboxamide, N-[(1R,2R)-2,3-bis(4-chlorophenyl)-1-methylpropyl]-5-fluoro-, rel-, mono(trifluoroacetate) (9CI)
MF C24 H20 Cl2 F N3 O . C2 H F3 O2

CM 1

Relative stereochemistry.



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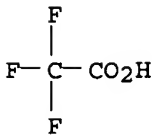
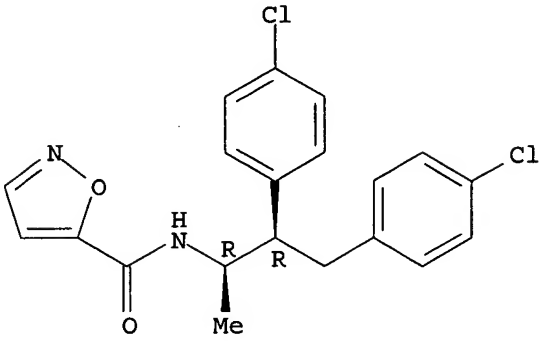


L66 187 ANSWERS REGISTRY COPYRIGHT 2005 ACS on STN
IN 5-Isoxazolecarboxamide, N-[(1R,2R)-2,3-bis(4-chlorophenyl)-1-methylpropyl]-, rel-, mono(trifluoroacetate) (9CI)

MF C20 H18 Cl2 N2 O2 . C2 H F3 O2

CM 1

Relative stereochemistry.



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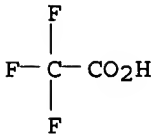
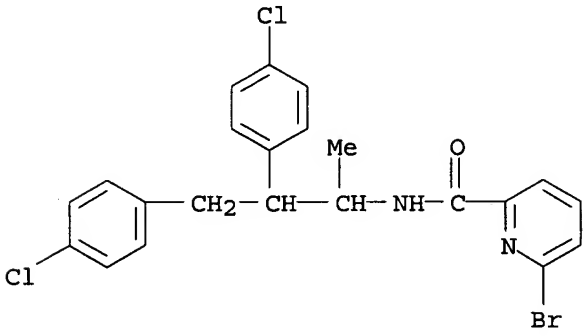


L66 187 ANSWERS REGISTRY COPYRIGHT 2005 ACS on STN
IN 2-Pyridinecarboxamide, N-[2,3-bis(4-chlorophenyl)-1-methylpropyl]-6-bromo-(9CI)
MF **C22 H19 Br Cl2 N2 O**

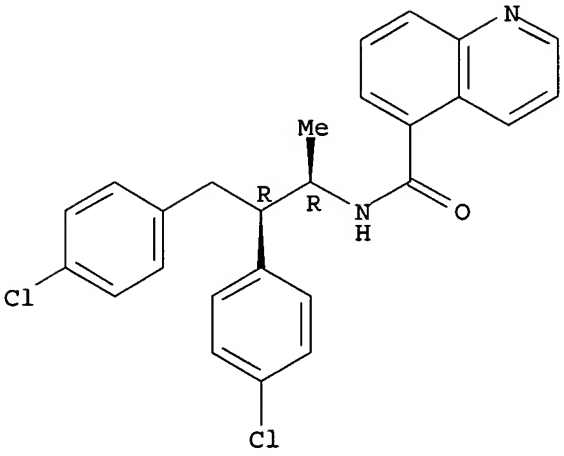


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L66 187 ANSWERS REGISTRY COPYRIGHT 2005 ACS on STN
IN 5-Quinolinecarboxamide, N-[(1R,2R)-2,3-bis(4-chlorophenyl)-1-methylpropyl]-, rel-, mono(trifluoroacetate) (9CI)
MF C26 H22 Cl2 N2 O . C2 H F3 O2

CM 1

Relative stereochemistry.



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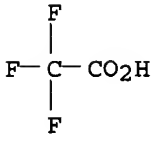
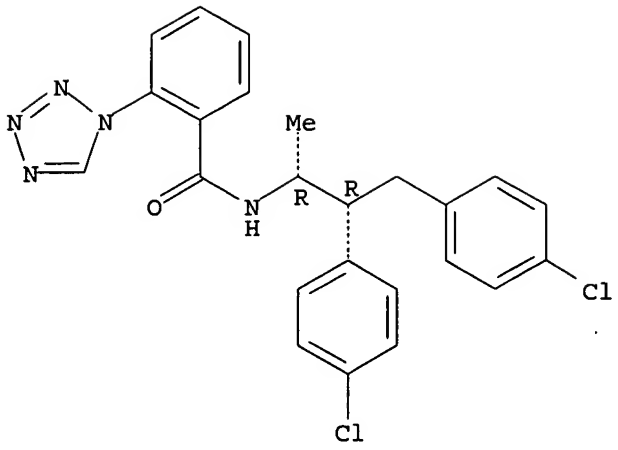


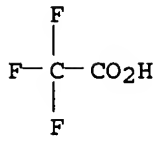
L66 187 ANSWERS REGISTRY COPYRIGHT 2005 ACS on STN
IN Benzamide, N-[(1R,2R)-2,3-bis(4-chlorophenyl)-1-methylpropyl]-2-(1H-tetrazol-1-yl)-, rel-, trifluoroacetate (9CI)
MF C24 H21 Cl2 N5 O . x C2 H F3 O2

CM 1

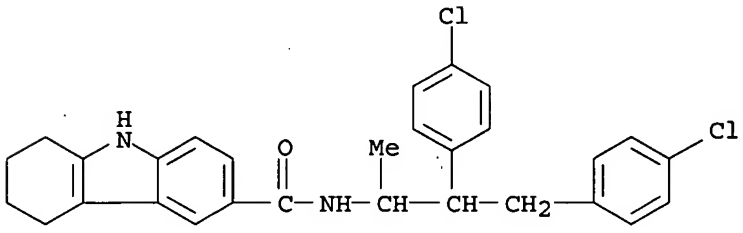
Relative stereochemistry.



CM 2



L66 187 ANSWERS REGISTRY COPYRIGHT 2005 ACS on STN
IN **1H-Carbazole-6-carboxamide, N-[2,3-bis(4-chlorophenyl)-1-methylpropyl]-2,3,4,9-tetrahydro- (9CI)**
MF **C29 H28 Cl2 N2 O**

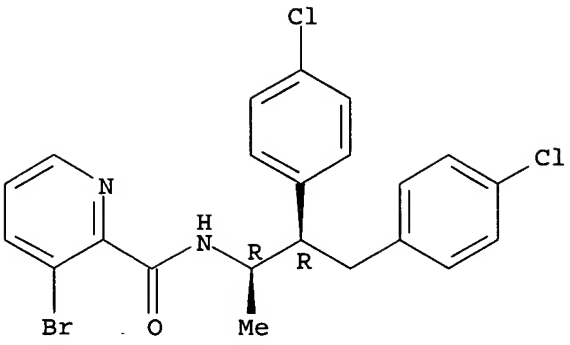


PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

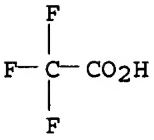
L66 187 ANSWERS REGISTRY COPYRIGHT 2005 ACS on STN
IN 2-Pyridinecarboxamide, N-[(1R,2R)-2,3-bis(4-chlorophenyl)-1-methylpropyl]-3-bromo-, rel-, mono(trifluoroacetate) (9CI)
MF C22 H19 Br Cl2 N2 O . C2 H F3 O2

CM 1

Relative stereochemistry.

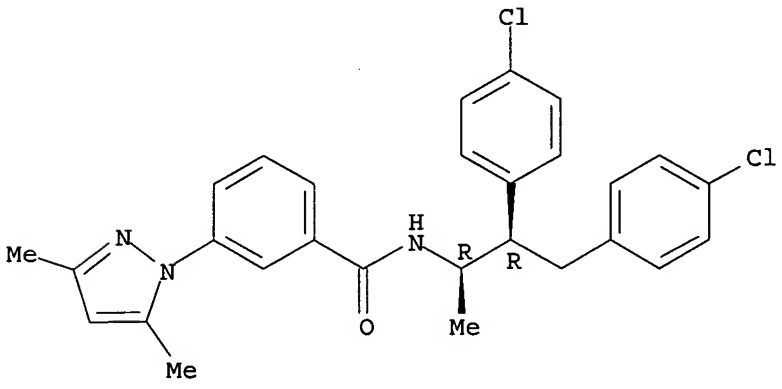


CM 2



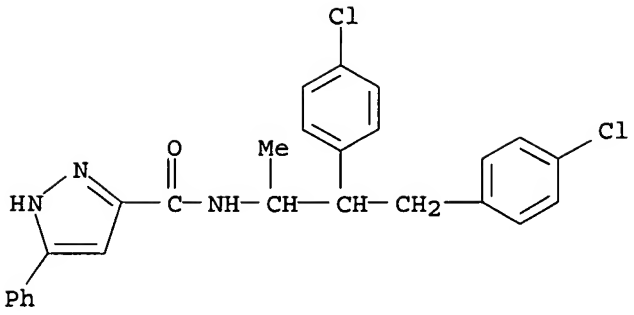
L66 187 ANSWERS REGISTRY COPYRIGHT 2005 ACS on STN
IN Benzamide, N-[(1R,2R)-2,3-bis(4-chlorophenyl)-1-methylpropyl]-3-(3,5-dimethyl-1H-pyrazol-1-yl)-, rel- (9CI)
MF C28 H27 Cl2 N3 O
CI COM

Relative stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

L66 187 ANSWERS REGISTRY COPYRIGHT 2005 ACS on STN
IN **1H-Pyrazole-3-carboxamide, N-[2,3-bis(4-chlorophenyl)-1-methylpropyl]-5-phenyl- (9CI)**
MF **C26 H23 Cl2 N3 O**



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

HOW MANY MORE ANSWERS DO YOU WISH TO SCAN? (1):end

=> d his

(FILE 'HCAPLUS' ENTERED AT 07:21:38 ON 28 SEP 2005)
DEL HIS

FILE 'REGISTRY' ENTERED AT 07:22:04 ON 28 SEP 2005

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L1           64 SEA FILE=REGISTRY ABB=ON  PLU=ON  (L*** OR L*** OR L*** OR L*** OR L
L2          285 SEA FILE=REGISTRY ABB=ON  PLU=ON  L*** NOT L***
L3            4 S L2 AND NCNC2/ES
L4            3 S L2 AND NCNC2-C6/ES
L5            2 S L2 AND SC4/ES
L6            2 S L2 AND NCSC2/ES
L7            2 S 616243-33-5 OR 616243-43-7
L8            2 S L2 AND CARBAZOL?
L9            1 S 616243-71-1
L10           1 S L8 AND 1/NC
L11           2 S L2 AND PYRIDO?
L12           4 S L2 AND PYRAZOL? AND PYRIMID?
L13           2 S L12 AND 2/NC
L14           2 S 616243-78-8 OR 616243-76-6
L15           2 S L12 AND 1/NC
L16           2 S L2 AND PYRIDO? AND PYRIMIDIN?
L17           2 S L2 AND IMIDAZO? AND PYRIDIN?
L18           1 S 616243-98-2
L19           1 S L17 AND 1/NC
L20           2 S L2 AND SC4-OC2OC2/ES
L21           6 S L2 AND NAPHTH?
L22           3 S L21 AND 2/NC
L23           3 S 616244-22-5 OR 616243-90-4 OR 616243-29-9
L24           3 S L21 AND 1/NC
L25          52 S L2 AND NC5/ES NOT L3-L24
L26          19 S L25 AND C6/ES AND NR>=3
L27           9 S L26 AND 1/NC
L28          10 S L26 NOT L27
L29           5 S 616243-35-7 OR 616243-53-9 OR 616243-55-1 OR 616243-57-3 OR 6
L30           5 S 616244-02-1 OR 616244-06-5 OR 616244-15-6 OR 616244-20-3 OR 6
L31          32 S L2 AND 46.150.18/RID AND 3/NR NOT L3-L30
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L32          23 S L31 AND 1/NC
L33          23 S L32 AND 4 CHLOROPHENYL
L34           8 S L33 AND BIS
L35          15 S L33 NOT L34
L36           9 S L31 NOT L32-L35
L37          32 S L2 AND 46.150.18/RID AND 4/NR NOT L3-L36
L38          14 S L37 AND 1/NC
L39          68 S L3,L4,L7,L9,L10,L14-L16,L18-L20,L23,L24,L27,L
L40          18 S L37 NOT L38,L39
L41           7 S 616244-28-1 OR 616244-32-7 OR 616244-12-3 OR 616244-24-7 OR 6
L42           9 S 616243-37-9 OR 616243-39-1 OR 616243-41-5 OR 616243-48-2 OR 6
L43          84 S L39,L41,L42
L44          63 S L1 AND 1/NC
L45         138 S L43,L44
                SEL RN
L46          42 S E1-E138/CRN
L47         179 S L45,L46
                SAV L47 KUMAR509B/A
L48         140 S L2 NOT L1,L3-L47

     FILE 'HCAOLD' ENTERED AT 08:40:41 ON 28 SEP 2005
L49           0 S L47

     FILE 'HCAPLUS' ENTERED AT 08:40:44 ON 28 SEP 2005
L50           1 S L47
                E HAGMANN/AU
                E HAGMANN 2/AU
                E HAGMANN W/AU
L51         180 S E3-E7
                E LIN L/AU
L52         279 S E3
                E LIN L S/AU
L53          27 S E3
                E LIN LINUS/AU
L54          29 S E3-E5
                E SHAH/AU
L55           1 S E3
                E SHAH S/AU
L56         148 S E3
L57          37 S E25
                E SHAH SHRENIK/AU
L58         101 S E3-E5
                E SHRENIK/AU
L59           1 S E4
                E KANTILAL/AU
L60           1 S L50 AND L51-L59
L61           1 S L50 AND MERCK?/PA,CS
L62           1 S L50,L60,L61

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L64         183 S L47,L63
L65           4 S 616244-18-9 OR 616243-94-8 OR 616243-92-6 OR 616243-31-3
L66         187 S L64,L65
                SAV L66 KUMAR509B/A

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L67           0 S L66
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     FILE 'HCAPLUS' ENTERED AT 08:45:32 ON 28 SEP 2005
L68             1 S L66
L69             1 S L62,L68

     FILE 'USPATFULL' ENTERED AT 08:45:41 ON 28 SEP 2005
L70             1 S L66

     FILE 'HCAPLUS' ENTERED AT 08:46:05 ON 28 SEP 2005

     FILE 'USPATFULL' ENTERED AT 08:46:20 ON 28 SEP 2005

     FILE 'REGISTRY' ENTERED AT 08:46:46 ON 28 SEP 2005

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Bib Data Sheet

CONFIRMATION NO. 7661

SERIAL NUMBER	FILING OR 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.
10/509,277	09/27/2004 RULE	564	1621	21071YP

APPLICANTS

William K. Hagmann, Westfield, NJ;
Linus S. Lin, Westfield, NJ;
Shrenik K. Shah, Metuchen, NJ;

** CONTINUING DATA ********

This application is a 371 of PCT/US03/09800 04/01/2003 which claims benefit of 60/370,553 04/05/2002

** FOREIGN APPLICATIONS ********

None

Foreign Priority claimed	STATE OR COUNTRY	SHEETS DRAWING	TOTAL CLAIMS	INDEPENDENT CLAIMS
☐ yes ☒ no	NJ		24	3
35 USC 119 (a-d) conditions met ☐ yes ☒ no ☐ Met after Allowance				
Verified and Acknowledged Examiner's Signature Initials				

ADDRESS

210

TITLE

Substituted aryl amides

FILING FEE RECEIVED	FEES: Authority has been given in Paper
802	No. _____ to charge/credit DEPOSIT ACCOUNT No. _____ for following:

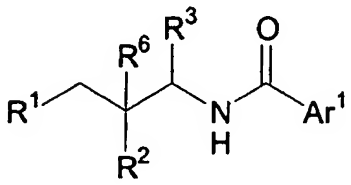
- ☐ All Fees
- ☐ 1.16 Fees (Filing)
- ☐ 1.17 Fees (Processing Ext. of time)
- ☐ 1.18 Fees (Issue)
- ☐ Other _____
- ☐ Credit

Amendments to the Claims:

This listing of claims will replace all prior versions and listings of claims in the present application.

Listing of Claims:

Claim 1 (currently amended): A compound of structural formula I:



(I)

or a pharmaceutically acceptable salt thereof, wherein;

R^1 is selected from:

(1) C_{1-10}alkyl,

(2) C_{3-10}cycloalkyl,

(3) cycloheteroalkyl,

(4) aryl, and

(5) heteroaryl,

wherein alkyl is optionally substituted with one, two, three or four substituents independently selected from R^a, and each cycloalkyl, cycloheteroalkyl, aryl and heteroaryl are optionally substituted on a carbon or nitrogen atom with one, two, three or four substituents independently selected from R^b;

R^2 is selected from:

(1) C_{3-10}cycloalkyl,

(2) cycloheteroalkyl,

(3) aryl,

(4) heteroaryl,

(5) $-OR^d$,

(6) $-NR^cR^d$, and

(7) $-CO_2R^d$,

wherein ~~each alkyl is optionally substituted with one, two, three or four substituents independently selected from R^a, and~~ each cycloalkyl, cycloheteroalkyl, aryl and heteroaryl are optionally substituted on a carbon or nitrogen atom with one, two, three or four substituents independently selected from R^b;

R^3 is ~~selected from:~~

~~(1) hydrogen, and~~

~~(2)~~ C_{1-4}alkyl,

wherein alkyl is optionally substituted with one to four substituents independently selected from R^a;

R^6 is selected from:

(1) hydrogen,

(2) C_{1-4}alkyl,

(3) C_{2-4}alkenyl,

(4) C_{2-4}alkynyl,

(5) $-OR^d$,

(6) halogen,

(7) -CN,

(8) $-NR^cR^d$,

wherein alkyl, alkenyl, and alkynyl are optionally substituted with one to four substituents independently selected from R^a

Ar^1 is selected from:

(1) aryl, and

(2) heteroaryl,

each optionally substituted on the carbon or nitrogen with one, two, or three groups independently selected from R^b;

each R^a is independently selected from:

(1) $-OR^c$,

(2) $-NR^cS(O)_mR^d$,

(3) $-NO_2$,

(4) halogen,

(5) $-S(O)_mR^c$,

(6) $-SR^c$,

(7) $-S(O)_2OR^c$,

(8) $-S(O)_mNR^cR^d$,

(9) $-NR^cR^d$,
(10) $-O(CR^eR^f)_nNR^cR^d$,
(11) $-C(O)R^c$,
(12) $-CO_2R^c$,
(13) $-CO_2(CR^eR^f)_nCONR^cR^d$,
(14) $-OC(O)R^c$,
(15) -CN,
(16) $-C(O)NR^cR^d$,
(17) $-NR^cC(O)R^d$,
(18) $-OC(O)NR^cR^d$,
(19) $-NR^cC(O)OR^d$,
(20) $-NR^cC(O)NR^cR^d$,
(21) $-CR^c(N-OR^d)$,
(22) CF_3,
(23) $-OCF_3$,
(24) C_{3-8}cycloalkyl,
(25) cycloheteroalkyl, and
(26) oxo;

each R^b is independently selected from:

(1) R^a,
(2) C_{1-10}alkyl,
(3) C_{3-8}cycloalkyl,
(4) cycloheteroalkyl,
(5) aryl,
(6) arylC_{1-4}alkyl,
(7) heteroaryl, and
(8) heteroarylC_{1-4}alkyl,

wherein alkyl, cycloalkyl, cycloheteroalkyl, and heteroaryl are optionally substituted with oxo, and wherein aryl and heteroaryl are optionally substituted with $-OR^c$, NR^cR^d, or $-C(O)R^c$;

R^c and R^d are independently selected from:

(1) hydrogen,
(2) C_{1-10}alkyl,
(3) C_{2-10}alkenyl,

(4) C_{2-10}alkynyl,
(5) cycloalkyl,
(6) cycloalkyl-C_{1-10}alkyl,
(7) cycloheteroalkyl,
(8) cycloheteroalkyl-C_{1-10} alkyl;
(9) aryl,
(10) heteroaryl,
(11) aryl-C_{1-10}alkyl, and
(12) heteroaryl-C_{1-10}alkyl, or

R^c and R^d together with the atom(s) to which they are attached form a heterocyclic ring of 4 to 7 members containing 0-2 additional heteroatoms independently selected from oxygen, sulfur and N-Rg,
or two -OR^c groups together with the atom(s) to which they are attached form a heterocyclic ring of 4 to 7 members containing 0-2 additional heteroatoms independently selected from oxygen, sulfur and N-Rg,
each R^c and R^d may be unsubstituted or substituted with one to three substituents selected from R^h;
R^e and R^f are independently selected from:

(1) hydrogen,
(2) C_{1-10}alkyl,
(3) C_{2-10} alkenyl,
(4) C_{2-10}alkynyl,
(5) cycloalkyl,
(6) cycloalkyl-C_{1-10} alkyl,
(7) cycloheteroalkyl,
(8) cycloheteroalkyl-C_{1-10} alkyl,
(9) aryl,
(10) heteroaryl,
(11) arylC_{1-10} alkyl, and
(12) heteroarylC_{1-10} alkyl, or

R^e and R^f together with the carbon to which they are attached form a ring of 5 to 7 members containing 0-2 heteroatoms independently selected from oxygen, sulfur and nitrogen;
each Rg is independently selected from

(1) C_{1-10}alkyl,
(2) C_{3-8}cycloalkyl,
(3) cycloheteroalkyl,

(4) aryl,
(5) arylC_{1-4}alkyl,
(6) heteroaryl,
(7) heteroarylC_{1-4}alkyl,
(8) $-S(O)_mR^e$,
(9) $-C(O)R^e$,
(10) $-CO_2R^e$,
(11) $-CO_2(CR^eR^f)_nCONR^eR^f$, and
(12) $-C(O)NR^eR^f$;

each R^h is independently selected from:

(1) C_{1-10}alkyl,
(2) C_{3-8}cycloalkyl,
(3) cycloheteroalkyl,
(4) aryl,
(5) arylC_{1-4}alkyl,
(6) heteroaryl,
(7) heteroarylC_{1-4}alkyl,
(8) $-OR^e$,
(9) $-NR^eS(O)_mR^f$,
(10) $-S(O)_mR^e$,
(11) $-SR^e$,
(12) $-S(O)_2OR^e$,
(13) $-S(O)_mNR^eR^f$,
(14) $-NR^eR^f$,
(15) $-O(CR^eR^f)_nNR^eR^f$,
(16) $-C(O)R^e$,
(17) $-CO_2R^e$,
(18) $-CO_2(CR^eR^f)_nCONR^eR^f$,
(19) $-OC(O)R^e$,
(20) $-CN$,
(21) $-C(O)NR^eR^f$,
(22) $-NR^eC(O)R^f$,
(23) $-OC(O)NR^eR^f$,

(24) -$NR^eC(O)OR^f$,

(25) -$NR^eC(O)NR^eR^f$,

(26) CF_3, and

(27) -OCF_3,

m is selected from 1 and 2; and

n is selected from 1, 2, and 3;

~~provided that when R^1 is phenyl, naphthyl, or heteroaryl, R^2 is phenyl and R^3 is hydrogen, then Ar^1 is not unsubstituted phenyl and is not mono, di or tri- substituted phenyl with an R^b substituent selected from the group consisting of halogen, hydroxy, C 1-6 alkyl, phenyl, -CN, NO_2, CO_2H, $C(O)C_{1-6}$alkyl, CO_2C_{1-6} alkyl, $C(O)NH_2$, C(O)NH heterocycloalkyl, NH_2, NH heterocycloalkyl, furanyl, dihydrofuranyl, pyrrolidyl, dihydropyrrolidyl, and 1,3-dioxolan; and~~

~~provided that when R^1 is aryl, monosubstituted with halogen, OCH_3 or CH_3 or optionally di-substituted with halogen, R^2 is aryl, optionally mono- or di- substituted with halogen, and R^3 is hydrogen, then Ar^1 is not unsubstituted 4-pyridinyl; and~~

provided that when R^1 and R^2 are unsubstituted aryl or unsubstituted heteroaryl, and R^3 is ~~hydrogen or~~ C 1-4 alkyl, then Ar^1 is substituted with at least one R^b substituent; and

provided that when R^1 is selected from the group consisting of unsubstituted phenyl, *para*-chlorophenyl or *para*–methoxy phenyl, R^2 is unsubstituted phenyl, and R^3 is $-CH_3$, then Ar^1 is not unsubstituted phenyl, *ortho*—CO_2H monosubstituted phenyl, or 3,4-dimethoxy phenyl.

Claim 2 (currently amended): The compound according to Claim 1 wherein:

R^1 is selected from:

(1) C_{1-10}alkyl,

(2) C_{3-10}cycloalkyl,

(3) cycloheteroalkyl,

(4) aryl, and

(5) heteroaryl,

wherein alkyl is optionally substituted with one, two, three or four substituents independently selected from R^a, and each cycloalkyl, cycloheteroalkyl, aryl and heteroaryl are optionally substituted with one, two, three or four substituents independently selected from R^b;

R^2 is selected from:

(1) C_{3-10}cycloalkyl,

(2) cycloheteroalkyl,

(3) aryl,

(4) heteroaryl,

(5) $-OR^d$,

(6) $-NR^cR^d$, and

(7) $-CO_2R^d$,

wherein ~~each alkyl is optionally substituted with one, two, three or four substituents independently selected from R^a, and~~ each cycloalkyl, and cycloheteroalkyl aryl and heteroaryl are optionally substituted with one, two, three or four substituents independently selected from R^b;

or a pharmaceutically acceptable salt thereof.

Claim 3 (Original): The compound according to Claim 2 wherein:

Ar^1 is selected from:

(1) phenyl,

(2) naphthyl,

(3) thienyl,

(4) furanyl,

(5) pyrrolyl,

(6) oxazolyl,

(7) isoxazolyl,

(8) 1,2,5-oxadiazolyl,

(9) 1,2,5-thiadiazolyl,

(10) thiazolyl,

(11) pyrazolyl,

(12) triazolyl,

(13) tetrazolyl,

(14) benzothienyl,

(15) benzofuranyl,

(16) benzoxazolyl,
(17) benzimidazolyl,
(18) benzothiazolyl,
(19) indanyl,
(20) indenyl,
(21) indolyl,
(22) imidazo[1,2-a]pyridinyl,
(23) β-carbolinyl,
(24) 5,6,7,8-tetrahydro-β-carbolinyl,
(25) tetrahydronaphthyl,
(26) 4,5,6,7-tetrahydroindazolyl,
(27) 2,3-dihydrobenzofuranyl,
(28) dihydrobenzopyranyl,
(29) 1,4-benzodioxanyl,
(30) pyridinyl,
(31) pyrimidinyl,
(32) pyrazinyl,
(33) quinolinyl,
(34) isoquinolinyl,
(35) quinazolonyl,
(36) quinazolinyl,
(37) 1,8-naphthyridinyl,
(38) 1,2,3,4-tetrahydro-1,8-naphthyridinyl,
(39) pyrido[3,2-b]pyridinyl,
(40) pyrazolo[2,3-a]pyrimidinyl,
(41) pyrido[1,2-a]pyrimidinyl,
(42) pyrido[1,2-a]pyrimidonyl,
(43) benzopyrimidinyl,
(44) imidazolyl, and
(45) imidazolonyl,

each optionally substituted with one, two, or three groups independently selected from R^b;

or a pharmaceutically acceptable salt thereof.

Claim 4 (Original): The compound according to Claim 3 wherein:

R^3 is C_{1-4}alkyl, optionally substituted with one to four substituents independently selected from R^a;

R^6 is selected from:

(1) hydrogen,

(2) methyl,

(3) hydroxyl,

(4) halogen, and

(5) -CN,

wherein methyl is optionally substituted with one to three R^a substituents;

Ar^1 is selected from:

(1) phenyl,

(2) naphthyl,

(3) thienyl,

(4) isoxazolyl,

(5) 1,2,5-oxadiazolyl,

(6) thiazolyl,

(7) pyrazolyl,

(8) triazolyl,

(9) tetrazolyl,

(10) benzofuranyl,

(11) benzoxazolyl,

(12) benzimidazolyl,

(13) benzothiazolyl,

(14) imidazo[1,2-a]pyridinyl,

(15) 5,6,7,8-tetrahydro-β-carbolinyl,

(16) 4,5,6,7-tetrahydroindazolyl,

(17) pyridinyl,

(18) pyrimidinyl,

(19) pyrazinyl,

(20) quinolinyl,

(21) isoquinolinyl,

(22) quinazolonyl,

(23) quinazolinyl,

(24) 1,8-naphthyridinyl,

(25) 1,2,3,4-tetrahydro-1,8-naphthyridinyl,

(26) pyrido[3,2-b]pyridinyl,

(27) pyrazolo[2,3-a]pyrimidinyl,

(28) pyrido[1,2-a]pyrimidinyl,

(29) pyrido[1,2-a]pyrimidonyl,

(30) benzopyrimidinyl,

(31) imidazolyl, and

(32) imidazolonyl,

each optionally substituted with one, two, or three groups independently selected from R^b;

each R^a is independently selected from:

(1) $-OR^c$,

(2) halogen,

(3) $-S(O)_mR^c$,

(4) $-SR^c$,

(5) $-S(O)_2OR^c$,

(6) $-S(O)_mNR^cR^d$,

(7) $-NR^cR^d$,

(8) $-C(O)R^c$,

(9) $-CO_2R^c$,

(10) -CN,

(11) $-C(O)NR^cR^d$,

(12) CF_3,

(13) $-OCF_3$,

(14) C_{3-8}cycloalkyl,

(15) cycloheteroalkyl, and

(16) oxo;

each R^b is independently selected from:

(1) R^a,

(2) C_{1-10}alkyl,

(3) cycloheteroalkyl,

(4) aryl,

(5) arylC_{1-4}alkyl,

(6) heteroaryl, and
(7) heteroarylC_{1-4}alkyl,

wherein alkyl, cycloalkyl, cycloheteroalkyl, heteroaryl are optionally substituted with oxo, and wherein aryl and heteroaryl are optionally substituted with -OR^c, NR^cR^d, or -$C(O)R^c$;

R^c and R^d are independently selected from:

(1) hydrogen,
(2) C_{1-10}alkyl,
(3) cycloalkyl,
(4) cycloheteroalkyl,
(5) aryl,
(6) heteroaryl, or

R^c and R^d together with the atom(s) to which they are attached form a heterocyclic ring of 4 to 7 members containing 0-2 additional heteroatoms independently selected from oxygen, sulfur and N-Rg,
or two -OR^c groups together with the atom(s) to which they are attached form a heterocyclic ring of 4 to 7 members containing 0-2 additional heteroatoms independently selected from oxygen, sulfur and N-Rg,
each R^c and R^d may be unsubstituted or substituted with one to three substituents selected from R^h;
or a pharmaceutically acceptable salt thereof.

Claim 5 (Original): The compound according to Claim 4 wherein:

R^1 and R^2 are independently selected from:

(1) phenyl, and
(2) pyridyl,

each optionally substituted with one to four substituents independently selected from R^b;
R^3 is C_{1-4}alkyl, wherein alkyl is optionally substituted with one to four substituents independently selected from R^a;
R^6 is selected from:

(1) hydrogen,
(2) methyl,
(3) hydroxyl,
(4) halogen, and
(5) –CN;

each R^a is independently selected from:

(1) -OR^c,

(2) halogen,
(3) $-S(O)_mR^c$,
(4) $-NR^cR^d$,
(5) $-C(O)R^c$,
(6) $-CO_2R^c$, and
(7) oxo;

or a pharmaceutically acceptable salt thereof.

Claim 6 (Original): The compound according to Claim 5 wherein:

R^1 and R^2 are independently selected from:

(1) phenyl,
(2) 4-fluorophenyl,
(3) 2-chlorophenyl,
(4) 3-chlorophenyl,
(5) 4-chlorophenyl,
(6) 4-cyanophenyl,
(7) 4-methylphenyl,
(8) 4-isopropylphenyl,
(9) 4-biphenyl,
(10) 4-bromophenyl,
(11) 4-iodophenyl,
(12) 2,4-dichlorophenyl, and
(13) 2-chloro-4-fluorophenyl;

or a pharmaceutically acceptable salt thereof.

Claim 7 (Original): The compound according to Claim 6 wherein:

R^1 and R^2 are independently selected from phenyl and 4-chlorophenyl;

R^3 is methyl, wherein methyl is optionally substituted with one to three substituents independently selected from R^a;

or a pharmaceutically acceptable salt thereof.

Claim 8 (Original): A compound selected from:

(1) N-(2,3-bis(4-chlorophenyl)-1-methylpropyl)-benzofuran-2-carboxamide;

(2) *N*-[2,3-bis(4-chlorophenyl)-1-methylpropyl]-3-chloro-2-naphthamide;

(3) N-(2,3-bis(4-chlorophenyl)-1-methylpropyl)-isoxazole-5-carboxamide;

(4) N-(2,3-bis(4-chlorophenyl)-1-methylpropyl)-pyrido[3,2-b]pyridine-2-carboxamide;

(5) N-(2,3-bis(4-chlorophenyl)-1-methylpropyl)-pyrazole-3-carboxamide;

(6) N-(2,3-bis(4-chlorophenyl)-1-methylpropyl)-thiazole-5-carboxamide;

(7) N-(2,3-bis(4-chlorophenyl)-1-methylpropyl)-nicotinamide;

(8) 2-(1-tetrazolyl)-N-(2,3-bis(4-chlorophenyl)-1-methylpropyl)-benzamide;

(9) 3-(1-tetrazolyl)-N-(2,3-bis(4-chlorophenyl)-1-methylpropyl)-benzamide;

(10) 4-(1-tetrazolyl)-N-(2,3-bis(4-chlorophenyl)-1-methylpropyl)-benzamide;

(11) 5-methyl-N-(2,3-bis(4-chlorophenyl)-1-methylpropyl)-thiazole-4-carboxamide;

(12) 2-phenyl-N-(2,3-bis(4-chlorophenyl)-1-methylpropyl)-benzamide;

(13) N-(2,3-bis(4-chlorophenyl)-1-methylpropyl)-pyrazine-2-carboxamide;

(14) 3-(1-(3,5-dimethyl-pyrazolyl))-N-(2,3-bis(4-chlorophenyl)-1-methylpropyl)-benzamide;

(15) 4-(1-(pyrrolidin-2-one))-N-(2,3-bis(4-chlorophenyl)-1-methylpropyl)-benzamide;

(16) 3-(1-(imidazolidin-2-one))-N-(2,3-bis(4-chlorophenyl)-1-methylpropyl)-benzamide;

(17) 4-phenyl-N-(2,3-bis(4-chlorophenyl)-1-methylpropyl)-benzamide;

(18) 6-bromo-N-(2,3-bis(4-chlorophenyl)-1-methylpropyl)-picolinamide;

(19) N-(2,3-bis(4-chlorophenyl)-1-methylpropyl)-isonicotinamide;

(20) N-(2,3-bis(4-chlorophenyl)-1-methylpropyl)-picolinamide;

(21) 4-methyl-N-(2,3-bis(4-chlorophenyl)-1-methylpropyl)-1,2,5-oxadiazole-3-carboxamide;

(22) 3-(1-(pyrrolidin-2-one))-N-(2,3-bis(4-chlorophenyl)-1-methylpropyl)-benzamide;

(23) 2-bromo-N-(2,3-bis(4-chlorophenyl)-1-methylpropyl)-isonicotinamide;

(24) 3-phenyl-N-(2,3-bis(4-chlorophenyl)-1-methylpropyl)-benzamide;

(25) N-(2,3-bis(4-chlorophenyl)-1-methylpropyl)-pyrimidine-4-carboxamide;

(26) 4-(1-pyrazolyl)-N-(2,3-bis(4-chlorophenyl)-1-methylpropyl)-benzamide;

(27) 2-(1-pyrazolyl)-N-(2,3-bis(4-chlorophenyl)-1-methylpropyl)-benzamide;

(28) 5,6,7,8-tetrahydro-N-(2,3-bis(4-chlorophenyl)-1-methylpropyl)-carbazole-3-carboxamide;

(29) N-(2,3-bis(4-chlorophenyl)-1-methylpropyl)-1H-quinazolin-2-one-4-carboxamide;

(30) N-(2,3-bis(4-chlorophenyl)-1-methylpropyl)-benzoxazole-2-carboxamide;

(31) N-(2,3-bis(4-chlorophenyl)-1-methylpropyl)-pyrazolo[2,3-a]pyrimidine-6-carboxamide;

(32) 2,4-dimethyl-N-(2,3-bis(4-chlorophenyl)-1-methylpropyl)-pyrazolo[2,3-a]pyrimidine-6-carboxamide;

(33) 4-(1-piperidinyl)-N-(2,3-bis(4-chlorophenyl)-1-methylpropyl)-benzamide;

(34) N-(2,3-bis(4-chlorophenyl)-1-methylpropyl)-pyrimidine-5-carboxamide;
(35) N-(2,3-bis(4-chlorophenyl)-1-methylpropyl)-pyrido(1,2-a)pyrimidine-4-one-5-carboxamide;
(36) 4,5,6,7-tetrahydro-N-(2,3-bis(4-chlorophenyl)-1-methylpropyl)-indazole-3-carboxamide;
(37) 5-fluoro-N-(2,3-bis(4-chlorophenyl)-1-methylpropyl)-benzimidazole-2-carboxamide;
(38) 5-phenyl-N-(2,3-bis(4-chlorophenyl)-1-methylpropyl)-pyrazole-3-carboxamide;
(39) 1,2,3,4-tetrahydro-N-(2,3-bis(4-chlorophenyl)-1-methylpropyl)-1,8-naphthyridine-7-carboxamide;
(40) 1-methyl-3-ethyl-N-(2,3-bis(4-chlorophenyl)-1-methylpropyl)-pyrazole-5-carboxamide;
(41) 1-methyl-3-propyl-N-(2,3-bis(4-chlorophenyl)-1-methylpropyl)-pyrazole-5-carboxamide;
(42) N-(2,3-bis(4-chlorophenyl)-1-methylpropyl)-quinoline-5-carboxamide;
(43) N-(2,3-bis(4-chlorophenyl)-1-methylpropyl)-imidazo(1,2-a)pyridine-2-carboxamide;
(44) N-(2,3-bis(4-chlorophenyl)-1-methylpropyl)-quinoline-4-carboxamide;
(45) 4-bromo-N-(2,3-bis(4-chlorophenyl)-1-methylpropyl)-nicotinamide;
(46) N-(2,3-bis(4-chlorophenyl)-1-methylpropyl)-isoquinoline-8-carboxamide;
(47) 3-bromo-N-(2,3-bis(4-chlorophenyl)-1-methylpropyl)-picolinamide;
(48) N-(2,3-bis(4-chlorophenyl)-1-methylpropyl)-isoquinoline-5-carboxamide;
(49) 4-(2-formyl-phenyl)-N-(2,3-bis(4-chlorophenyl)-1-methylpropyl)-benzamide;
(50) 4-(2-hydroxymethyl-phenyl)-N-(2,3-bis(4-chlorophenyl)-1-methylpropyl)-benzamide;
(51) 4-(2-aminophenyl)-N-(2,3-bis(4-chlorophenyl)-1-methylpropyl)-benzamide;
(52) N-(2,3-bis(4-chlorophenyl)-1-methylpropyl)-2(3H)-imidazolone-4-carboxamide;
(53) 3-(1-tetrazolyl)-N-(2,3-bis(4-chlorophenyl)-1-methylpropyl)-isonicotinamide;
(54) 3,4-(ethylenedioxy)-N-(2,3-bis(4-chlorophenyl)-1-methylpropyl)-thiophene-2-carboxamide;
(55) 1-isopropyl-N-(2,3-bis(4-chlorophenyl)-1-methylpropyl)-pyrazole-4-carboxamide;
(56) 5-bromo-N-(2,3-bis(4-chlorophenyl)-1-methylpropyl)-picolinamide;
(57) N-(2,3-bis(4-chlorophenyl)-1-methylpropyl)-1,8-naphthyridine-2-carboxamide;
(58) N-(2,3-bis(4-chlorophenyl)-1-methylpropyl)-benzothiazole-2-carboxamide;
(59) N-(2,3-bis(4-chlorophenyl)-1-methylpropyl)-benzimidazole-2-carboxamide;
(60) 5-chloro-2-(2-(1-pyrrolyl)ethyl)-N-(2,3-bis(4-chlorophenyl)-1-methylpropyl)-benzamide;
(61) 2-(2-phenylethyl)-N-(2,3-bis(4-chlorophenyl)-1-methylpropyl)-benzamide;
(62) N-(2,3-bis(4-chlorophenyl)-1-methylpropyl)-naphthylene-2-carboxamide;
(63) N-(2,3-bis(4-chlorophenyl)-1-methylpropyl)-quinoline-5-carboxamide;
(64) N-(2,3-bis(4-chlorophenyl)-1-methylpropyl)-naphthylene-1-carboxamide;
(65) N-(2,3-bis(4-chlorophenyl)-1-methylpropyl)-benzamide;
(66) 2-chloro-N-(2,3-bis(4-chlorophenyl)-1-methylpropyl)-benzamide;

(67) 3-chloro-N-(2,3-bis(4-chlorophenyl)-1-methylpropyl)-benzamide;

(68) 4-chloro-N-(2,3-bis(4-chlorophenyl)-1-methylpropyl)-benzamide;

(69) 3,5-dichloro-N-(2,3-bis(4-chlorophenyl)-1-methylpropyl)-isonicotinamide;

(70) *N*-[2-(3-pyridyl)-3-(4-chlorophenyl)-1-methylpropyl]-benzamide;

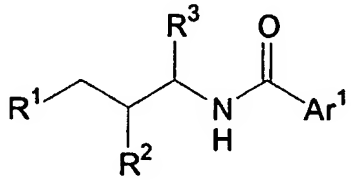
(71) *N*-[2-(2-pyridyl)-3-(4-chlorophenyl)-1-methylpropyl]-benzamide;

(72) *N*-[2-(4-pyridyl)-3-(4-chlorophenyl)-1-methylpropyl]-benzamide; and

(73) *N*-[3-(3-chloro-2-pyridyl)-2-phenyl-1-methylpropyl]-benzamide;

or a pharmaceutically acceptable salt thereof.

Claim 9 (currently amended): A compound of structural formula IA:



(IA)

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is selected from:

(1) aryl, and

(2) heteroaryl,

wherein aryl and heteroaryl are optionally substituted on the carbon or nitrogen with one to four substituents independently selected from R^b;

R^2 is selected from:

(1) aryl, and

(2) heteroaryl,

wherein aryl and heteroaryl are optionally substituted on the carbon or nitrogen with one to four substituents independently selected from R^b;

R^3 is ~~selected from:~~

~~(1) hydrogen, and~~

~~(2)~~ C_{1-4}alkyl,

wherein alkyl is optionally substituted with one to four substituents independently selected from R^a;

Ar^1 is selected from:

(1) aryl, and

(2) heteroaryl,

each optionally substituted on the carbon or nitrogen with one, two, or three groups independently selected from R^b;

each R^a is independently selected from:

(1) $-OR^c$,

(2) $-NR^cS(O)_mR^d$,

(3) $-NO_2$,

(4) halogen,

(5) $-S(O)_mR^c$,

(6) $-SR^c$,

(7) $-S(O)_2OR^c$,

(8) $-S(O)_mNR^cR^d$,

(9) $-NR^cR^d$,

(10) $-O(CR^eR^f)_nNR^cR^d$,

(11) $-C(O)R^c$,

(12) $-CO_2R^c$,

(13) $-CO_2(CR^eR^f)_nCONR^cR^d$,

(14) $-OC(O)R^c$,

(15) -CN,

(16) $-C(O)NR^cR^d$,

(17) $-NR^cC(O)R^d$,

(18) $-OC(O)NR^cR^d$,

(19) $-NR^cC(O)OR^d$,

(20) $-NR^cC(O)NR^cR^d$,

(21) $-CR^c(N\text{-}OR^d)$,

(22) CF_3,

(23) $-OCF_3$,

(24) C_{3-8}cycloalkyl,

(25) cycloheteroalkyl, and

(26) oxo;

each R^b is independently selected from:

(1) R^a,
(2) C_{1-10}alkyl,
(3) C_{3-8}cycloalkyl,
(4) cycloheteroalkyl,
(5) aryl,
(6) arylC_{1-4}alkyl,
(7) heteroaryl, and
(8) heteroarylC_{1-4}alkyl,

wherein alkyl, cycloalkyl, cycloheteroalkyl, and heteroaryl are optionally substituted with oxo, and wherein aryl and heteroaryl are optionally substituted with -OR^c, NR^cR^d, or -$C(O)R^c$;

R^c and R^d are independently selected from:

(1) hydrogen,
(2) C_{1-10}alkyl,
(3) C_{2-10} alkenyl,
(4) C_{2-10}alkynyl,
(5) cycloalkyl,
(6) cycloalkyl-C_{1-10}alkyl,
(7) cycloheteroalkyl,
(8) cycloheteroalkyl-C_{1-10} alkyl;
(9) aryl,
(10) heteroaryl,
(11) aryl-C_{1-10}alkyl, and
(12) heteroaryl-C_{1-10}alkyl, or

R^c and R^d together with the atom(s) to which they are attached form a heterocyclic ring of 4 to 7 members containing 0-2 additional heteroatoms independently selected from oxygen, sulfur and N-Rg,
or two -OR^c groups together with the atom(s) to which they are attached form a heterocyclic ring of 4 to 7 members containing 0-2 additional heteroatoms independently selected from oxygen, sulfur and N-Rg,
each R^c and R^d may be unsubstituted or substituted with one to three substituents selected from R^h;
R^e and R^f are independently selected from:

(1) hydrogen,
(2) C_{1-10}alkyl,
(3) C_{2-10} alkenyl,
(4) C_{2-10}alkynyl,

(5) cycloalkyl,
(6) cycloalkyl-C_{1-10} alkyl,
(7) cycloheteroalkyl,
(8) cycloheteroalkyl-C_{1-10} alkyl,
(9) aryl,
(10) heteroaryl,
(11) arylC_{1-10} alkyl, and
(12) heteroarylC_{1-10} alkyl, or

R^e and R^f together with the carbon to which they are attached form a ring of 5 to 7 members containing 0-2 heteroatoms independently selected from oxygen, sulfur and nitrogen;

each Rg is independently selected from

(1) C_{1-10}alkyl,
(2) C_{3-8}cycloalkyl,
(3) cycloheteroalkyl,
(4) aryl,
(5) arylC_{1-4}alkyl,
(6) heteroaryl,
(7) heteroarylC_{1-4}alkyl,
(8) $-S(O)_mR^e$,
(9) $-C(O)R^e$,
(10) $-CO_2R^e$,
(11) $-CO_2(CR^eR^f)_nCONR^eR^f$, and
(12) $-C(O)NR^eR^f$;

each R^h is independently selected from:

(1) C_{1-10}alkyl,
(2) C_{3-8}cycloalkyl,
(3) cycloheteroalkyl,
(4) aryl,
(5) arylC_{1-4}alkyl,
(6) heteroaryl,
(7) heteroarylC_{1-4}alkyl,
(8) $-OR^e$,
(9) $-NR^eS(O)_mR^f$,

(10) $-S(O)_mR^e$,

(11) $-SR^e$,

(12) $-S(O)_2OR^e$,

(13) $-S(O)_mNR^eR^f$,

(14) $-NR^eR^f$,

(15) $-O(CR^eR^f)_nNR^eR^f$,

(16) $-C(O)R^e$,

(17) $-CO_2R^e$,

(18) $-CO_2(CR^eR^f)_nCONR^eR^f$,

(19) $-OC(O)R^e$,

(20) -CN,

(21) $-C(O)NR^eR^f$,

(22) $-NR^eC(O)R^f$,

(23) $-OC(O)NR^eR^f$,

(24) $-NR^eC(O)OR^f$,

(25) $-NR^eC(O)NR^eR^f$,

(26) CF_3, and

(27) $-OCF_3$,

m is selected from 1 and 2; and

n is selected from 1, 2, and 3;

~~provided that when R^1 is phenyl, naphthyl, or heteroaryl, R^2 is phenyl and R^3 is hydrogen, Ar^1 is not unsubstituted phenyl and is not mono, di or tri- substituted phenyl with an R^b substituent selected from the group consisting of halogen, hydroxy, C_{1-6} alkyl, phenyl, -CN, $-NO_2$, $-CO_2H$, $-C(O)C_{1-6}$alkyl, $-CO_2C_{1-6}$ alkyl, $-C(O)NH_2$, $-C(O)NH$-heterocycloalkyl, $-NH_2$, -NH-heterocycloalkyl, furanyl, dihydrofuranyl, pyrrolidyl, dihydropyrrolidyl, and 1,3-dioxolan; and~~

~~provided that when R^1 is aryl, monosubstituted with halogen, $-OCH_3$ or $-CH_3$ and optionally di-substituted with halogen, R^2 is aryl, optionally mono- or di- substituted with halogen, and R^3 is hydrogen, Ar^1 is not unsubstituted 4-pyridinyl; and~~

provided that when R^1 and R^2 are unsubstituted aryl or unsubstituted heteroaryl, and R^3 is ~~hydrogen or~~ C_{1-4} alkyl, Ar^1 is substituted with at least one R^b substituent; and

provided that when R^1 is selected from the group consisting of unsubstituted phenyl, *para*-chlorophenyl or *para*–methoxy phenyl, R^2 is unsubstituted phenyl, and R^3 is $-CH_3$, Ar^1 is not unsubstituted phenyl, *ortho*—CO_2H monosubstituted phenyl, or 3,4-dimethoxy phenyl.

Claim 10 (Original): The compound according to Claim 9 wherein:
R^1 and R^2 are independently selected from:

(1) phenyl,
(2) naphthyl, and
(3) pyridyl,

each optionally substituted with one to four substituents independently selected from R^b;
or a pharmaceutically acceptable salt thereof.

Claim 11 (Original): The compound according to Claim 10 wherein:
Ar^1 is selected from:

(1) phenyl,
(2) naphthyl,
(3) thienyl,
(4) furanyl,
(5) pyrrolyl,
(6) oxazolyl,
(7) isoxazolyl,
(8) 1,2,5-oxadiazolyl,
(9) 1,2,5-thiadiazolyl,
(10) thiazolyl,
(11) pyrazolyl,
(12) triazolyl,
(13) tetrazolyl,
(14) benzothienyl,
(15) benzofuranyl,
(16) benzoxazolyl,

(17) benzimidazolyl,
(18) benzothiazolyl,
(19) indanyl,
(20) indenyl,
(21) indolyl,
(22) imidazo[1,2-a]pyridinyl,
(23) β-carbolinyl,
(24) 5,6,7,8-tetrahydro-β-carbolinyl,
(25) tetrahydronaphthyl,
(26) 4,5,6,7-tetrahydroindazolyl,
(27) 2,3-dihydrobenzofuranyl,
(28) dihydrobenzopyranyl,
(29) 1,4-benzodioxanyl,
(30) pyridinyl,
(31) pyrimidinyl,
(32) pyrazinyl,
(33) quinolinyl,
(34) isoquinolinyl,
(35) quinazolonyl,
(36) quinazolinyl,
(37) 1,8-naphthyridinyl,
(38) 1,2,3,4-tetrahydro-1,8-naphthyridinyl,
(39) pyrido[3,2-b]pyridinyl,
(40) pyrazolo[2,3-a]pyrimidinyl,
(41) pyrido[1,2-a]pyrimidinyl,
(42) pyrido[1,2-a]pyrimidonyl,
(43) benzopyrimidinyl,
(44) imidazolyl, and
(45) imidazolonyl,

each optionally substituted with one, two, or three groups independently selected from R^b; or a pharmaceutically acceptable salt thereof.

Claim 12 (currently amended): The compound of claim 11 wherein:

R^3 is ~~selected from:~~

~~(1) hydrogen, and~~

~~(2)~~ C_{1-4}alkyl,

wherein alkyl is optionally substituted with one to four substituents independently selected from R^a;

Ar^1 is selected from:

(1) phenyl,
(2) naphthyl,
(3) thienyl,
(4) isoxazolyl,
(5) 1,2,5-oxadiazolyl,
(6) thiazolyl,
(7) pyrazolyl,
(8) triazolyl,
(9) tetrazolyl,
(10) benzofuranyl,
(11) benzoxazolyl,
(12) benzimidazolyl,
(13) benzothiazolyl,
(14) imidazo[1,2-a]pyridinyl,
(15) 5,6,7,8-tetrahydro-β-carbolinyl,
(16) 4,5,6,7-tetrahydroindazolyl,
(17) pyridinyl,
(18) pyrimidinyl,
(19) pyrazinyl,
(20) quinolinyl,
(21) isoquinolinyl,
(22) quinazolonyl,
(23) quinazolinyl,
(24) 1,8-naphthyridinyl,
(25) 1,2,3,4-tetrahydro-1,8-naphthyridinyl,
(26) pyrido[3,2-b]pyridinyl,
(27) pyrazolo[2,3-a]pyrimidinyl,
(28) pyrido[1,2-a]pyrimidinyl,

(29) pyrido[1,2-a]pyrimidonyl,

(30) benzopyrimidinyl,

(31) imidazolyl, and

(32) imidazolonyl,

each optionally substituted with one, two, or three groups independently selected from R^b;

each R^a is independently selected from:

(1) $-OR^c$,

(2) halogen,

(3) $-S(O)_mR^c$,

(4) $-SR^c$,

(5) $-S(O)_2OR^c$,

(6) $-S(O)_mNR^cR^d$,

(7) $-NR^cR^d$,

(8) $-C(O)R^c$,

(9) $-CO_2R^c$,

(10) -CN,

(11) $-C(O)NR^cR^d$,

(12) CF_3,

(13) $-OCF_3$,

(14) C_{3-8}cycloalkyl,

(15) cycloheteroalkyl, and

(16) oxo;

each R^b is independently selected from:

(1) R^a,

(2) C_{1-10}alkyl,

(3) cycloheteroalkyl,

(4) aryl,

(5) arylC_{1-4}alkyl,

(6) heteroaryl, and

(7) heteroarylC_{1-4}alkyl,

wherein alkyl, cycloalkyl, cycloheteroalkyl, heteroaryl are optionally substituted with oxo, and

wherein aryl and heteroaryl are optionally substituted with $-OR^c$, NR^cR^d, or $-C(O)R^c$;

R^c and R^d are independently selected from:

(1) hydrogen,
(2) C_{1-10}alkyl,
(3) cycloalkyl,
(4) cycloheteroalkyl,
(5) aryl,
(6) heteroaryl, or

R^c and R^d together with the atom(s) to which they are attached form a heterocyclic ring of 4 to 7 members containing 0-2 additional heteroatoms independently selected from oxygen, sulfur and N-Rg,
or two -OR^c groups together with the atom(s) to which they are attached form a heterocyclic ring of 4 to 7 members containing 0-2 additional heteroatoms independently selected from oxygen, sulfur and N-Rg,
each R^c and R^d may be unsubstituted or substituted with one to three substituents selected from R^h;
or a pharmaceutically acceptable salt thereof.

Claim 13 (Original): The compound according to Claim 12, wherein:
R^1 and R^2 are independently selected from:

(1) phenyl, and
(2) pyridyl,

each optionally substituted with one to four substituents independently selected from R^b;
R^3 is C_{1-4}alkyl, wherein alkyl is optionally substituted with one to four substituents independently selected from R^a;
each R^a is independently selected from:

(1) -OR^c,
(2) halogen,
(3) -$S(O)_mR^c$,
(4) -NR^cR^d,
(5) -$C(O)R^c$,
(6) -CO_2R^c, and
(7) oxo;

or a pharmaceutically acceptable salt thereof.

Claim 14 (Original): The compound according to Claim 13, wherein:
R^1 and R^2 are independently selected from:

(1) phenyl,

(2) 4-fluorophenyl,
(3) 2-chlorophenyl,
(4) 3-chlorophenyl,
(5) 4-chlorophenyl,
(6) 4-cyanophenyl,
(7) 4-methylphenyl,
(8) 4-isopropylphenyl,
(9) 4-biphenyl,
(10) 4-bromophenyl,
(11) 4-iodophenyl,
(12) 2,4-dichlorophenyl, and
(13) 2-chloro-4-fluorophenyl;
or a pharmaceutically acceptable salt thereof.

Claim 15 (Original): The compound according to Claim 14 wherein:
R^1 and R^2 are independently selected from phenyl and 4-chlorophenyl;
R^3 is methyl, wherein methyl is optionally substituted with one to three substituents independently selected from R^a;
or a pharmaceutically acceptable salt thereof.

Claim 16 (Original): A composition comprising a compound according to Claim 1 and a pharmaceutically acceptable carrier.

Claim 17 (Original): A composition comprising a compound according to Claim 8 and a pharmaceutically acceptable carrier.

Claim 18 (Original): A method of preventing obesity in a person at risk for obesity comprising administration to said person of about 0.001 to about 100 mg/kg of a compound according to Claim 1.

Claim 19 (Original): A method of preventing obesity in a person at risk for obesity comprising administration to said person of about 0.001 to about 100 mg/kg of a compound according to Claim 8.

Claim 20 (Original): A method of treating a disease mediated by the Cannabinoid-1 receptor comprising administration of a therapeutically effective amount of a compound of Claim 1 to a patient in need of such treatment.

Claim 21 (Original): The method according to Claim 20 wherein the disease mediated by the Cannabinoid-1 receptor is selected from: psychosis, memory deficit, cognitive disorders, migraine, neuropathy, neuro-inflammatory disorders, cerebral vascular accidents, head trauma, anxiety disorders, stress, epilepsy, Parkinson's disease, schizophrenia, substance abuse disorders, constipation, chronic intestinal pseudo-obstruction, cirrhosis of the liver, asthma, obesity, and other eating disorders associated with excessive food intake.

Claim 22 (Original): The method according to Claim 21 wherein the disease mediated by the Cannabinoid-1 receptor is an eating disorder associated with excessive food intake.

Claim 23 (Original): The method according to Claim 22 wherein the eating disorder asssociated with excessive food intake is selected from obesity, bulimia nervosa, and compulsive eating disorders.

Claim 24 (Original): The method according to Claim 23 wherein the eating disorder associated with excessive food intake is obesity.

Claims 25-30 (Cancelled).

REMARKS

Reconsideration of the present application in view of the remarks below and the amendments above is respectfully requested.

Claims 1-24 were pending in this application. Claims 1-7 and 9-24 were rejected. Claim 8 was found allowable. Claims 1, 2, 9, and 12 have been amended. Presently, Claims 1 to 24 remain under consideration in the present application.

Claim 1 has been amended to delete the phrase "each alkyl is optionally substituted with one, two, three or four substituents independently selected from R^a, and" from the definition of R^2. Also, the spelling of "alky" has been corrected to "alkyl" in R^1. Still further, consistent with each of the exemplified compounds, R^3 has been amended to be optionally substituted C_{1-4} alkyl, by the deletion of the element "hydrogen" from the Markush group, and provisos affecting compounds wherein R^3 is hydrogen have been deleted. Support for the deletion of hydrogen is found in originally filed Claim 4, and in the specification at page 15, lines 26 to 28. These amendments do not add new matter to the present application.

Claim 2 has been amended to delete the phrase "each alkyl is optionally substituted with one, two, three or four substituents independently selected from R^a, and" from the definition of R^2. Also, the spelling of "alky" has been corrected to "alkyl" in R^1. These amendments do not add new matter to the present application.

Claim 9 has been amended to define R^3 as optionally substituted C_{1-4} alkyl, by the deletion of the element "hydrogen" from the Markush group. This is consistent with each of the exemplified compounds, wherein R^3 is alkyl. Support for the deletion of hydrogen is found in originally filed Claim 13, and in the specification at page 15, lines 26 to 28. Additionally, provisos affecting compounds wherein R^3 is hydrogen have been deleted. Still further, the semicolon following "wherein" in the line after structural formula IA, has been replaced with a colon. These amendments do not add new matter to the present application.

Claim 12 has been amended to delete the element "hydrogen" from the Markush group for R^3 and thereby define R^3 as optionally substituted C_{1-4} alkyl. Support for the deletion of hydrogen is found in originally filed Claim 13, and in the specification at page 15, lines 26 to 28. This amendment does not add new matter to the present application.

Claim Rejections – 35 USC §112

Claims 1-7 were rejected under 35 USC § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as their invention. The

Examiner stated that Claim 1 defined R^2 to be various groups but the alkyl, and at the same time depicts that each alkyl is substituted with various substituents, thus rendering claims indefinite.

Applicants have amended Claims 1 and 2 to delete the phrase "each alkyl is optionally substituted with one, two, three or four substituents independently selected from R^a, and" from the definition of R^2. These amendments do not add new matter to the present application.

As amended, the Claims 1 and 2, together with dependent Claims 3-7, are definite and particularly point out and distinctly claim the subject matter which Applicants regard as their invention

In view of the amendments and remarks above, Applicants respectfully request reconsideration and withdrawal of the rejection of Claims 1-7 under 35 USC § 112, second paragraph.

Claim Rejections – 35 USC §103

Claims 1-7 and 9-24 were rejected under 35 USC § 103(a) as being unpatentable over GB 899556. The Examiner stated that GB'556 teaches structurally similar compounds, composition and method of use as claimed herein, for example, page 1, column 1, lines 10-20. The Examiner asserted that it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made obtain compounds within the generic disclosure of the reference, because they are structurally so similar to those claimed herein, with the reasonable expectation of achieving a successful pharmaceutical composition, for treating tumors, absent evidence to the contrary, and further noted that R^1 and R^2 in the reference can be halo and methyl or halo and methoxy, thus not covered by the proviso.

Applicants have amended Claims 1, 9, and 12 to define R^3 as optionally substituted C_{1-4} alkyl, by the deletion of the element "hydrogen" from the Markush group. Claims 2-7, and 10-24, which depend directly or indirectly from Claim 1 or Claim 9, respectively, incorporate this limitation.

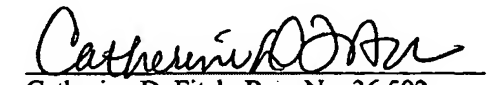
GB '556 does not teach or suggest or motivate one of ordinary skill in the art to arrive at the presently compounds having an alkyl group at the R^3 position, compositions comprising these compounds, and methods of treating and preventing diseases and conditions mediated by the cannabinoid 1 receptor. GB '556 describes substituted isonicotinic acid amides having a hydrogen substituent on the carbon adjacent to the nitrogen of the amide useful for treating tumors. There is no suggestion or motivation for one of ordinary skill in the art to modify the compounds of GB '556 to alkylate at the carbon adjacent to the nitrogen of the amide for any purpose, neither to obtain compounds useful for treating tumors, nor to treat or prevent cannabinoid 1 receptor mediated diseases and conditions. GB '556 does not teach or suggest or motivate one of ordinary skill in the art to arrive at the presently compounds having an alkyl group at the R^3 position,

compositions comprising these compounds, and methods of treating and preventing diseases and conditions mediated by the cannabinoid 1 receptor.

In view of the amendments and remarks above, Applicants respectfully request reconsideration and withdrawal of the rejection of Claims 1-7, and 9-24 under 35 USC § 103(a) over GB 899556.

Applicants respectfully request reconsideration and withdrawal of the rejection and earnestly solicit a favorable response from the Examiner. The Examiner is invited to contact Applicants' representative at the number below, if such contact would facilitate prosecution of this application to allowance.

Respectfully submitted,

By 

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December 14, 2005

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/509,277	09/27/2004	William K. Hagmann	21071YP	7661

210 7590 09/15/2005

MERCK AND CO., INC
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EXAMINER	
KUMAR, SHAILENDRA	
ART UNIT	**PAPER NUMBER**
1621	

DATE MAILED: 09/15/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/509,277	HAGMANN ET AL.	
	Examiner	Art Unit	
	SHAILENDRA -. KUMAR	1621	

– The MAILING DATE of this communication appears on the cover sheet with the correspondence address –

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 September 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *8* is/are allowed.

6)☒ Claim(s) *1-7 and 9-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/17/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-24 are pending in this application.

Information Disclosure Statement

1. The information disclosure statement (IDS) submitted on 12/17/2004 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 1-7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 defines R2 to be various groups but the alkyl, and at the same time depicts that each alkyl is substituted with various substituents, thus rendering claims indefinite.

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

6. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 1-7 and 9-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over GB 899556.

GB"556 teaches structurally similar compounds, composition and method of use as claimed herein. See for example, page 1, column 1, lines 10-20. The difference between the reference and herein claimed compounds is that the reference has not made specific compounds as claimed herein.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to obtain compounds within the generic disclosure of the

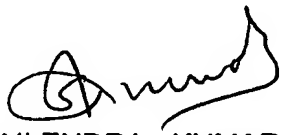
reference, because they are structurally so similar to those claimed herein, with the reasonable expectation of achieving a successful pharmaceutical composition, for treating tumors, absent evidence to the contrary. Note that R1 and R2 in the reference can be halo and methyl or halo and methoxy, thus not covered by the proviso.

8. Claim 8 appears to be free of prior art and is allowable.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to SHAILENDRA -. KUMAR whose telephone number is (571)272-0640. The examiner can normally be reached on Mon-Thur 8:00-5:30, Alt Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on (571)272-0646. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



SHAILENDRA - KUMAR
Primary Examiner
Art Unit 1621

S.Kumar
9/14/05

PATENT SPECIFICATION

NO DRAWINGS

899,550

Date of Application and filing Complete Specification: June 12, 1959.

No. 20266/59.

Application made in Germany (No. 25947) on June 12, 1958.

Complete Specification Published: June 27, 1962.

Index at acceptance:—Class 2(8), C1C(3:4:8:9:11D:11F), C1F1(A1:B:C4:D3), C1F2(C4:D2), C1H1(A1:B:C2).

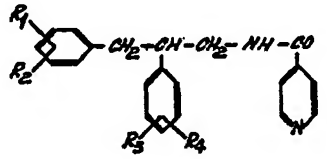
International Classification:—C07d.

COMPLETE SPECIFICATION

Substituted Isonicotinic Acid Amides and process for their manufacture

We, FARBWERKE HOECHST AKTIENGESELLSCHAFT vormals Meister Lucius & Brüning, a body corporate recognised under German law, of Frankfurt (Main)—Höchst, Germany, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

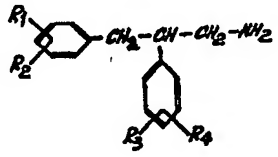
The present invention provides new substituted isonicotinic acid amides of the general formula



in which R_1 represents a halogen atom or a methyl or methoxy, R_2 and R_3 each represent a hydrogen or halogen atom, and R_4 represents a halogen atom.

The new compounds are valuable medicaments and have the special property of being capable of inhibiting the growth of tumors.

The invention also provides a process for the manufacture of the isonicotinic acid amides of the above formula, wherein a substituted 2:3-diphenyl-propylamine of the general formula



in which R_1, R_2, R_3 and R_4 have the meanings given above, is reacted with isonicotinic acid or a reactive derivative thereof.

As examples of amines used as starting materials in the process there may be mentioned: 2:3 - di - (4^1 - chlorophenyl)-propylamine, 2 - (4^1 - chlorophenyl) - 3-(3^{11}:4^{11} - dichlorophenyl) - propylamine, 2-(3^1:4^1 - dichlorophenyl) - 3 - (4^{11} - chlorophenyl) - propylamine, 2 - (4^1 - chlorophenyl) - 3 - (2^{11}:4^{11} - dichlorophenyl)-propylamine, 2:3 - di - (3^1:4^1 - dichlorophenyl) - propylamine, 2 - (2^1:4^1 - dichlorophenyl) - 3 - (4^{11} - chlorophenyl) - propylamine, 2 - (4^1 - chlorophenyl) - 3 - (4^{11}-fluorophenyl) - propylamine, 2 - (4^1 - chlorophenyl) - 3 - (4^{11} - bromophenyl) - propylamine, 2 - (4^1 - chlorophenyl) - 3 - (4^{11}-methoxyphenyl) - propylamine and 2-(2^1:4^1 - dichlorophenyl) - 3 - (4^{11} - methylphenyl)-propylamine.

These amines may be obtained, for example, by reacting an appropriately substituted benzaldehyde or benzyl halide, in the presence of an alkaline condensing agent, with a substituted benzyl-cyanide, and then reducing the substituted α:β-diphenyl-acrylonitriles or α:β-diphenyl-propionitriles thus obtained, by a method in itself known.

The process may, for example, be carried out by reacting the hydrohalic acid salt of a reactive derivative, for example, a halide, of the isonicotinic acid such, for example, as isonicotinic acid chloride hydrochloride, in the presence of a basic compound, for example, a tertiary organic base such as pyridine, dimethyl aniline, triethylamine or an inorganic basically reacting salt such as potassium or sodium carbonate, and a solvent, with the substituted 2:3-diphenyl-propylamine. Advantageously the acid that is liberated is bound by means of pyridine, the latter being added in excess so that it is simultaneously used as solvent. The reaction is carried out at a normal or slightly below normal temperature.

In an alternative procedure an ester of isonicotinic acid, for example the ethyl ester thereof, is used as the reactive derivative. The reaction is then advantageously carried out by

mixing the isonicotinic acid ester with the amine and then heating the mixture at an elevated temperature, preferably at a temperature within the range of 180 to 250° C.

In a further alternative method isonicotinic acid is reacted with the substituted 2:3-diphenyl-propylamine by mixing, for example, equimolecular proportions of the acid and the amine and, completing the reaction, by heating the salt thus obtained for a short time in an open flask at an elevated temperature, preferably at a temperature within the range of 270—320° C., until no more water is split off.

Most of the new isonicotinic acid amides of this invention are colourless to yellowish solid compounds. Some of them can only be obtained as yellow, very viscous oils.

The compounds of the invention inhibit the growth of malignant tumors, and in this respect some of them are markedly superior to the known compounds of analogous structure. Apart from affording an absolutely higher *dosis tolerata* they have a higher chemotherapeutic index with respect to certain transplantation tumors than the known cytostatica. The isonicotinic acid 2-(3^1:4^1-dichlorophenyl)-3-(4^{11}-chlorophenyl)propylamide, for example, substantially inhibits the growth of tumors. This compound is effective, for example, in the case of a transplantable benzpyrene sarcoma of the golden hamster, whereas here the known cytostatica (ethylene imine derivatives, such as Thio-TEPA, TEM (registered Trade Mark), ethylene imine quinones and nitrogen mustard oxide) are completely ineffective. In the case of the transplantable benzpyrene sarcoma of the mouse, the compound is also more effective than the above mentioned known preparations.

The following Table I summarizes the test results of some products of the present invention and compares them with those obtained with thiophosphoric acid triethylene imide which is a cytostaticum known by the name of "Thio-TEPA":

TABLE I

Compound	(a)	(b)	(c)	Thio-TEPA
Dosis maxima tolerata per 20 g of mouse	100 mg subcutaneously, 25 mg per os	100 mg subcutaneously, 100 mg per os	50 mg subcutaneously, 30 mg per os	0.2 mg subcutaneously
Dosis therapeutica per 20 g of mouse	4×25 mg subcutaneously, 4×6.25 mg per os	4×25 mg subcutaneously, 4×25 mg per os	4×12.5 mg subcutaneously, 4×8 mg per os	4×0.05 mg subcutaneously
Tumours:				
solid Ehrlich carcinoma	+	+	(+) / +	(+) / +
sarcoma induced subcutaneously by means of methylcholanthrene	++/+++	++		++/+++
transplantable benzopyrene sarcoma of the golden hamster	(+) / +			no effect
dosis therapeutica per 100 g of the golden hamster	4×50 mg subcutaneously 4×12.5 mg per os			

(a) = isonicotinic acid-2-(3^1:4^1-dichlorophenyl)-3-(4^{11}-chlorophenyl)-*n*-propylamide

(b) = isonicotinic acid-2-(4^1-chlorophenyl)-3-(4^{11}-methoxyphenyl)-*n*-propylamide

(c) = isonicotinic acid-2:3-di-(4^1-chlorophenyl)-*n*-proplyamide

Each test result was determined by treating the tumor with the indicated dosis therapeutica of the particular product. The symbols used in the Table have the following meanings:

(+) means a 10—25% inhibition of the tumor as compared with the untreated controls.

+ means a 25—50% inhibition of the tumor as compared with the untreated controls.

+!+ means a 50—75% inhibition of the tumor as compared with the untreated controls.

+!+!+ means a 75—100% inhibition of the tumor as compared with the untreated controls.

The compounds of the invention may be used as such or as galenical preparations thereof, for example as tablets, capsules, dragees, ampoules, oily or aqueous solutions or suspensions or crystal suspensions, in admixture or conjunction with the usual pharmaceutical, organic or inorganic and physiologically tolerable carriers. As such carriers there are used those compounds which do not react with the compounds of the invention, for example water, gelatine, bolus, lactose, starch, magnesium stearate, talcum, tylose, vegetable oils such as olive oil, peanut oil, castor oil, cotton seed oil or neat's foot oil, or gum, propylene glycol, polyethylene glycol, zinc oxide or titanium dioxide. The compounds of the present invention or the corresponding galenical preparations thereof may be sterilized and/or may contain assistants such as stabilizers, buffers, wetting agents, emulsifiers or salts influencing the osmotic pressure. The galenicals are prepared by methods in themselves known. The compound of the invention may be added to the galenical preparation in a dosage of 0.1—10%. The human dosage is within the range of 0.2—2 grams per day.

The following Examples illustrate the invention:—

EXAMPLE 1.

Isonicotinic acid - [2:3 - di - (4^1 - chlorophenyl) - propyl] - amide

13.5 Grams of isonicotinic acid were heated with 28 grams of 2:3-di-(4^1-chlorophenyl)-propylamine in an open vessel for 5 minutes at 300—310° C. (bath temperature). Water was split off with effervescence. The still warm melt was dissolved in 30 cc of ethanol and then filtered. On cooling, 18.8 g of isonicotinic acid - [2:3 - di - (4^1 - chlorophenyl) - propyl] - amide melting at 126° C., crystallized.

EXAMPLE 2.

Isonicotinic acid - [2 - (4^1 - chlorophenyl)-3 - (4^{11} - fluorophenyl) - propyl] - amide

24.4 Grams of isonicotinic acid and 47 grams of 2 - (4^1 - chlorophenyl) - 3 - (4^{11}-fluorophenyl)-propylamine were mixed and the mixture was heated in an open vessel for 5 minutes at 300—310° C. The still warm melt was dissolved in a little warm ethanol, and then filtered. About five times the quantity of diisopropyl ether was then added to the filtrate. 37 grams of crude isonicotinic acid - [2 - (4^1 - chlorophenyl) - 3 - (4^{11}-fluorophenyl)-propyl]-amide were obtained, and the product could be purified by dissolving in benzene and reprecipitating with petroleum ether. The compound melted at 115—116° C.

EXAMPLE 3.

Isonicotinic acid - [2 - (3^1:4^1 - dichlorophenyl) - 3 - (4^{11} - chlorophenyl) - propyl]-amide

33.5 Grams of isonicotinic acid and 78 grams of 2 - (3^1:4^1 - dichlorophenyl) - 3-(4^{11} - chlorophenyl) - propylamine were heated for 5 minutes in an open vessel at 300 to 310° C. The cooled melt was dissolved in 100 cc of ethanol on a steam bath, filtered and then water was added to the warm solution until it became turbid. After cooling and filtering the solution under suction, 66 grams of isonicotinic acid - [2 - (3^1:4^1 - dichlorophenyl) - 3 - (4^{11} - chlorophenyl) - propyl]-amide were obtained.

The product was purified by recrystallization from ethanol/water. The pure compound was a colourless powder melting at 137—138° C.

EXAMPLE 4.

Isonicotinic acid - [2 - (4^1 - chlorophenyl)-3-(2^1:4^1-dichlorophenyl)-propyl]-amide

27 Grams of isonicotinic acid and 62.9 grams of 2 - (4^1 - chlorophenyl) - 3-(2^{11}:4^{11} - dichlorophenyl) - propylamine were mixed and then heated in an open vessel for 5 minutes at 290—310° C. The cooled melt was dissolved in 100 cc of warm ethanol, filtered and the filtrate was mixed with 500 cc of diisopropyl ether. On standing in the refrigerator, the product crystallized. 64 grams of isonicotinic acid - [2 - (4^1 - chlorophenyl) - 3 - (2^{11}:4^{11} - dichlorophenyl)-propyl]-amide were thus obtained. The compounds could be purified by recrystallization from benzene. It then melted at 139—140° C.

EXAMPLE 5.

Isonicotinic acid - [2 - (4^1 - chlorophenyl)-3-(4^{11}-methoxyphenyl)-propyl]-amide

27 Grams of isonicotinic acid and 55.1 grams of 2 - (4^1 - chlorophenyl) - 3 - (4^{11}-methoxyphenyl)-propylamine were heated in an open vessel for 5 minutes at 300—310° C. The still warm melt was dissolved in a little ethanol, then filtered and the isonicotinic acid-[2 - (4^1 - chlorophenyl) - 3 - (4^{11} - methoxyphenyl) - propyl] - amide was precipitated by addition of diisopropyl ether. The compound, which melted at 125° C., was obtained in a yield of 58 grams. The melting point was no different after recrystallization from benzene/petroleum ether.

EXAMPLE 6.

Isonicotinic acid - [2:3 - bis - (3^1:4^1 - dichlorophenyl)-propyl]-amide

13 Grams of isonicotinic acid and 35 grams of 2:3 - bis - (3^1:4^1 - dichlorophenyl)-propylamine were mixed and then heated in an open vessel for 10 minutes at 300—310° C. After cooling, the melt was dissolved in 150 cc of alcohol. The oil that separated after addition of a little water, solidified slowly on prolonged standing. After filtering under suction, 35 grams of a yellowish product were obtained. The isonicotinic acid-[2:3-bis-(3^1:4^1 - dichlorophenyl) - propyl]amide thus obtained could be purified by recrystallization from benzene/diisopropyl ether and then melted at 146—148° C.

By using 13 grams of isonicotinic acid and 28 grams of 2 - (4^1 - chlorophenyl) - 3-(2^{11}-chlorophenyl)-propylamine, and conducting the process in an analogous manner, 28 grams of isonicotinic acid-[2-(4^1-chlorophenyl) - 3 - (2^{11} - chlorophenyl) - propyl]-amide were obtained. After recrystallization from benzene/diisopropyl ether the product melted at 117—118° C.

EXAMPLE 7.

Isonicotinic acid - [2 - (2^1:4^1 - dichlorophenyl) - 3 - (4^{11} - chlorophenyl) - propyl]-amide

13 Grams of isonicotinic acid and 31.5 grams of 2 - (2^1:4^1 - dichlorophenyl) - 3-(4^{11}-chlorophenyl)-propylamine were mixed and then heated for 5 to 10 minutes at 300—310° C. The cooled melt was dissolved in 150 cc of benzene and the undissolved material was removed by filtration. After adding a little petroleum ether, 26 grams of isonicotinic acid - [2 - (2^1:4^1 - dichlorophenyl) - 3 - (4^{11} - chlorophenyl) - propyl]-amide crystallized out. By recrystallization from benzene/petroleum ether, a colourless powder melting at 117—118° C. was obtained.

EXAMPLE 8.

Isonicotinic acid - [2 - (4^1 - chlorophenyl)-3-(3^{11}-chlorophenyl)-propyl]-amide

27 Grams of isonicotinic acid and 56 grams of 2 - (4^1 - chlorophenyl) - 3 - (3^{11} - chlorophenyl)-propylamine were mixed and then heated in an open vessel for 5 minutes at 300—310° C. The cooled melt was dissolved in chloroform, the solution was washed with dilute hydrochloric acid, then with a dilute sodium hydroxide solution and then with water, dried over sodium sulphate and finally distilled under reduced pressure. Isonicotinic acid - [2 - (4^1 - chlorophenyl) - 3 - (3^{11}-chlorophenyl) - propyl] - amide distilled at 305—310° C. under a pressure of 3 mm of mercury as a very viscous, yellow oil.

EXAMPLE 9.

Isonicotinic acid - [2 - (4^1 - chlorophenyl)-3-(3^{11}:4^{11}-dichlorophenyl)-propyl]-amide

27 Grams of isonicotinic acid and 62.7 grams of 2 - (4^1 - chlorophenyl) - 3-(3^{11}:4^{11} - dichlorophenyl) - propylamine was heated for 5 minutes at 300—310° C. The cooled melt was dissolved in chloroform, washed with dilute hydrochloric acid, then with dilute sodium hydroxide solution and then with water, dried over sodium sulphate and, after evaporating the solvent, distilled under reduced pressure. 47 grams of isonicotinic acid - [2 - (4^1 - chlorophenyl) - 3-(3^{11}:4^{11} - dichlorophenyl) - propyl] - amide boiling at 308—312° C. under a pressure of 2 mm Hg were obtained.

EXAMPLE 10.

Isonicotinic acid - [2 - (3^1:4^1 - dichlorophenyl) - 3 - (4^{11} - methoxyphenyl)-propyl]-amide

45 Grams of isonicotinic acid and 109 grams of 2 - (3^1:4^1 - dichlorophenyl) - 3-(4^{11} - methoxyphenyl) - propylamine were heated together for 10 minutes at 300 to 310° C. The cooled melt was dissolved in benzene, washed with water and then dried. On distillation of the reaction product, a very viscous, brown compound boiling at 315—320° C. under a pressure of 1.7 mm Hg was obtained in a yield of 77 grams.

EXAMPLE 11.

Isonicotinic acid - [2 - (4^1 - chlorophenyl)-3-(4^{11}-bromophenyl)-propyl]-amide

A mixture of 14.5 grams of isonicotinic acid and 35 grams of 2-(4^1-chlorophenyl)-3-(4^{11} - bromophenyl) - propyl - amine was heated in an open vessel for 5 minutes at 290—300° C. The cooled melt was dissolved in 50 cc of ethanol. The product was crystallized by adding 500 cc of diisopropyl ether. 34 grams of isonicotinic acid-[2-(4^1-chlorophenyl) - 3 - (4^1 - bromophenyl) - propyl]-amide were obtained, and the product could be recrystallized from a mixture of ethyl acetate and diisopropyl ether (in a ratio of 1:2). The compound melted at 134—135° C.

EXAMPLE 12.

Isonicotinic acid - [2 - (4^1 - chlorophenyl)-3-(4^{11}-methylphenyl)-propyl]-amide

27 Grams of isonicotinic acid and 52 grams of 2 - (4^1 - chlorophenyl) - 3 - (4^{11} - methylphenyl)-propylamine were heated in an open vessel for 5 minutes at 300—310° C. The still warm melt was dissolved in 50 cc of ethanol. On cooling the solution, 55 grams of isnicotinic acid - [2 - (4^1 - chlorophenyl) - 3 - (4^{11}-methylphenyl) - propyl] - amide crystallized out. The compound could be purified by recrystallization from dilute ethanol and then melted at 133—134° C.

EXAMPLE 13.

Isonicotinic acid - [2:3 - di - (2^1:4^1 - dichlorophenyl)-propyl]-amide

34.9 Grams of 2:3-di-(2^1:4^1-dichlorophenyl)-propylamine and 13 grams of isonicotinic acid were heated together in an open vessel for 10 minutes at 300—310° C. The melt, which solidified on cooling to a glass

was taken up in ether, the ether solution was washed with water and then with a sodium bicarbonate solution, dried over sodium sulphate, and the solvent was then evaporated. On treating with petroleum ether the residue crystallized after standing for some days. Crystallization could be promoted by seeding. 30 grams of isonicotinic acid-[2:3-di-(2^1:4^1-di - chlorophenyl) - propyl] - amide were obtained as a yellowish compound that could be purified by recrystallization from acetonitrile and then melted at 128—130° C.

EXAMPLE 14.

Isonicotinic acid - [2 - (3^1:4^1 - dichlorophenyl) - 3 - (4^{11} - chlorophenyl) - propyl]-amide

63 Grams of 2 - (3^1:4^1 - dichlorophenyl)-3-(4^{11}-chloro-phenyl)-propylamine and 30.2 grams of isonicotinic acid ethyl ester were heated together in a flask that has an attached cooling tube, for 6 hours at 200—220° C. The cooled melt was dissolved in 50 cc of ethanol and then 500 cc of diisopropyl ether were added. 41 Grams of isonicotinic acid-[2 - (3^1:4^1 - dichloro - phenyl) - 3 - (4^{11}-chlorophenyl)-propyl]-amide crystallize out and, after recrystallization from ethanol/water, the compound melted at 138—139° C.

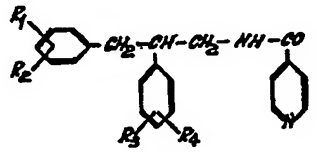
EXAMPLE 15.

Isonicotinic acid - [2 - (3^1:4^1 - dichlorophenyl) - 3 - (4^{11} - chlorophenyl) - propyl]-amide.

63 Grams of 2-(3^1:4^1-dichlorophenyl)-3-(4^{11} - chloro - phenyl) - propylamine were dissolved in 150 cc of pyridine and then 40 grams of isonicotinic acid chloride hydrochloride were added to the solution while cooling with ice. The mixture thus obtained was heated for 30 minutes on a steam bath and then poured into 4 litres of water, whereupon the product precipitated and solidified after some time. After filtering the product under suction, washing with water and air-drying 77 grams of isonicotinic acid-[2-(3^1:4^1 - dichlorophenyl) - 3 - (4^1 - dichlorophenyl)-propyl]-amide were obtained. After recrystallization from ethanol/water the compound melted at 138—139° C.

WHAT WE CLAIM IS:—

1. Substituted isonicotinic acid amides of the general formula



in which R_1 represents a halogen atom or a methyl or methoxy group, R_2 and R_3 each represent a hydrogen or halogen atom, and R_4 represents a halogen atom.

2. Isonicotinic acid - [2:3 - di - (4^1-chlorophenyl)-propyl]-amide.

3. Isonicotinic acid - [2 - (4^1 - chlorophenyl) - 3 - (4^{11} - fluorophenyl) - propyl]-amide.

4. Isonicotinic acid - [2 - (3^1:4^1 - dichlorophenyl) - 3 - (4^{11} - chlorophenyl)-propyl]-amide.

5. Isonicotinic acid - [2 - (4^1 - chlorophenyl) - 3 - (2^{11}:4^{11} - dichlorophenyl)-propyl]-amide.

6. Isonicotinic acid - [2 - (4^1 - chlorophenyl) - 3 - (4^{11} - methoxyphenyl) - propyl]-amide.

7. Isonicotinic acid - [2:3 - bis - (3^1:4^1-dichlorophenyl) - propyl] - amide.

8. Isonicotinic acid - [2 - 2^1:4^1 - dichlorophenyl) - 3 - (4^{11} - chlorophenyl) - propyl]-amide.

9. Isonicotinic acid - [2 - (4^1 - chlorophenyl) - 3 - (3^{11} - chlorophenyl) - propyl]-amide.

10. Isonicotinic acid - [2 - (4^1 - chlorophenyl) - 3 - (3^{11}:4^{11} - dichlorophenyl)-propyl]-amide.

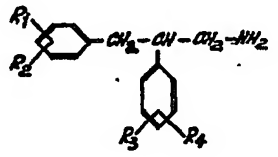
11. Isonicotinic acid - [2 - (3^1:4^1 - dichlorophenyl) - 3 - (4^{11} - methoxy - phenyl)-propyl]-amide.

12. Isonicotinic acid - [2 - (4^1 - chlorophenyl) - 3 - (4^1 - bromophenyl) - propyl]-amide.

13. Isonicotinic acid - [2 - (4^1 - chlorophenyl) - 3 - (4^{11} - methylphenyl) - propyl]-amide.

14. Isonicotinic acid - [2:3 - di - (2^1:4^1-dichlorophenyl)-propyl]-amide.

15. A process for the manufacture of substituted isonicotinic acid amides of the general formula given in claim 1, wherein a substituted 2:3-diphenyl-propylamine of the general formula



in which R_1, R_2, R_3 and R_4 have the meaning given in claim 1 is reacted with isonicotinic acid or with a reactive derivatve thereof.

16. A process as claimed in claim 15, wherein the salt obtained by reacting isonicotinic acid with a 2:3-diphenyl-propylamine of the formula given in claim 15 is heated at a temperature within the range of 270—320° C., until no more water is split off.

17. A process as claimed in claim 15, wherein an isonicotinic acid ester is heated with a substituted 2:3-diphenyl-propylamine of the formula given in claim 15, at a temperature within the range of 180° C. and 250° C.

18. A pharmaceutical preparation which comprises a compound claimed in any one of claims 1—14 in admixture or conjunction with a pharmaceutically suitable carrier.

19. A process for the manufacture of isonicotinic acid amides of the general formula given in claim 1, conducted substantially as described in any one of the Examples herein.

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